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## Unexplained Mortality During the U.S. COVID-19 Pandemic: Retrospective Analysis of Death Certificate Data and Critical Assessment of Excess Death Calculations

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-050361
Article Type:	Original research
Date Submitted by the Author:	18-Feb-2021
Complete List of Authors:	Fairman, Kathleen; Midwestern University College of Pharmacy - Glendale, Department of Pharmacy Practice; Kathleen Fairman LTD Goodlet, Kellie; Midwestern University College of Pharmacy - Glendale, Department of Pharmacy Practice Rucker, James; Kathleen Fairman LTD Zawadzki, Roy; University of California Irvine
Keywords:	COVID-19, EPIDEMIOLOGY, MENTAL HEALTH, PUBLIC HEALTH, STATISTICS & RESEARCH METHODS, Health informatics < BIOTECHNOLOGY & BIOINFORMATICS

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Unexplained Mortality During the U.S. COVID-19 Pandemic:  
Retrospective Analysis of Death Certificate Data and Critical Assessment of  
Excess Death Calculations

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Word count: 1559   Tables: 1   Figures: 1   Appendix: 1

Keywords: COVID-19, mortality, death certification, epidemiological methods, mental health

Abstract

Objectives: Cause-of-death discrepancies are common in respiratory illness-related mortality. A standard epidemiological metric, excess all-cause death, is unaffected by these discrepancies but provides no actionable policy information when increased all-cause mortality is unexplained by reported specific causes. To assess interpretability of the excess-death metric, we parsed excess deaths in the coronavirus-2019 (COVID-19) pandemic into explained versus unexplained causes.

Design: Retrospective repeated cross-sectional analysis of U.S. death-certificate data for 6 influenza seasons beginning October 2014, comparing population-adjusted historical benchmarks from the previous 2, 3, and 5 seasons with 2019-20.

Setting: 48 of 50 states with complete mortality data.

Participants: 16.3 million deaths in 312 weeks, reported in categories—all causes, top 8 natural causes, and respiratory causes including COVID-19—with no category for psychiatric-cause deaths.

Outcome Measures: Change in population-adjusted counts of deaths from seasonal benchmarks to 2019-20, from all causes (i.e., total excess deaths) and from explained versus unexplained causes, reported for the season overall and for time periods defined *a priori*: pandemic awareness (January 19 through March 28); initial pandemic peak (March 29 through May 30); and pandemic post-peak (May 31 through September 26).

Results: Of 287,957-306,267 excess all-cause deaths through September 2020, 179,903 (58.7%-62.5%, depending on seasonal benchmark) were attributed to COVID-19 and 44,022-49,311 (15.2%-16.1%) to other reported causes; 64,032-77,054 (22.2%-25.2%) were unexplained (unspecified or unreported cause). Unexplained deaths constituted 65.2%-72.5% of total mortality increase from January 19 to March 28.

Conclusions: Unexplained mortality contributed substantially to U.S. pandemic-period excess deaths. Onset of unexplained mortality in February 2020 coincided with previously reported increases in psychotropic use, suggesting possible psychiatric causes. Because true underlying causes of unexplained deaths may vary by group or region, results suggest limited interpretability of excess death calculations, supporting previous calls for improved cause-of-death data to support evidence-based policy decisions.

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**Article Summary**

Although the excess all-cause death metric has been reported extensively during the pandemic to indicate the mortality impact of coronavirus (COVID)-19, this is the first study to describe vulnerability of the calculation when a substantial proportion of excess mortality is unexplained by reported specific causes.

Because the true underlying causes of unexplained deaths likely vary by region or demographic group, the excess-death metric is of limited value to policy makers in the context of the COVID-19 pandemic, in which the mortality effects of policy decisions rather than the virus alone have been questioned.

We used population-adjusted U.S. national data, accounting for deaths in every category reported by the National Center for Health Statistics, including top natural causes and respiratory causes including COVID-19.

Our analysis was descriptive, but our estimates of all-cause excess deaths are similar to those previously developed using more sophisticated statistical analyses.

Study results generalize to the United States through September 26, 2020, but not to other countries, as cause-of-death attribution practices vary cross-nationally, or to other pandemic periods, including the COVID-19 case surge in late 2020.

## 99 Introduction

100 Errors in cause-of-death attribution (CODA) are common in infectious respiratory  
101 illness, compromising accurate tracking of disease impact and spread.<sup>1-3</sup> CODA is  
102 especially challenging in coronavirus disease 2019 (COVID-19) because of competing  
103 causes of mortality, including cancer, lung disease, obesity-related conditions, and  
104 superannuation.<sup>4</sup> Compounding this problem, methods for distinguishing COVID-19  
105 from competing causes vary substantially by country, making cross-national  
106 comparisons of COVID-19-attributed mortality problematic.<sup>3</sup>

107 A standard metric generally understood to account for these discrepancies is  
108 “excess death,” defined as mortality from all causes exceeding that expected from  
109 historical experience.<sup>5</sup> Recent investigators have calculated excess deaths to estimate  
110 U.S. COVID-19 impact, using death certificate data made available by the U.S. National  
111 Center for Health Statistics (NCHS).<sup>5-7</sup> The calculation has the advantages of no  
112 reliance on CODA, because it considers only all-cause deaths, and of accounting for  
113 deaths due to undetected COVID-19 or to use of scarce health system resources by  
114 infected patients.<sup>5-6</sup>

115 Despite these advantages, the utility and interpretation of excess death  
116 calculations may be compromised by unexplained deaths. Unlike full adjudicated death  
117 certificate files, which report all specific diagnosis codes causing or contributing to  
118 death, currently available NCHS pandemic-period files report 8 top causes of natural  
119 death and infectious causes, including COVID-19, in broad diagnostic categories  
120 (Supplement Appendix 1).<sup>8-11</sup> For excess deaths unexplained by these causes, the true  
121 underlying causes are unknown, despite presumably representing appropriate policy

122 targets. For example, markedly different interventions would be suggested by  
123 unexplained deaths due to undetected COVID-19, high-speed automobile accidents on  
124 empty highways,<sup>12</sup> or delayed care for life-threatening conditions when people fear  
125 using available emergency department capacity.<sup>13</sup>

126 Risk factors for potential causes of unexplained death vary cross-nationally. For  
127 example, U.S. opioid supplies, opioid mortality, substance use disorder prevalence, and  
128 suicide rates far exceed those of other high-income nations,<sup>14</sup> suggesting greater  
129 psychological vulnerability to pandemic-period disruptions. Yet, neither substance  
130 misuse nor mental illness is recorded as a cause of death in available NCHS files.<sup>8-11</sup>  
131 Risk factors for COVID-19 mortality, such as obesity, smoking, and healthcare  
132 associated infections, also demonstrate considerable cross-national variability.<sup>14</sup>

133 Quantifying unexplained excess deaths would provide information about the  
134 degree to which excess death calculations are potentially vulnerable to these disparate  
135 underlying risk factors. Moreover, assessing the timing of unexplained deaths at various  
136 pandemic phases would inform current discussions about societal factors that may  
137 contribute to pandemic-period morbidity and mortality, such as fear of contagion or  
138 economic vulnerability.<sup>15-17</sup> Accordingly, we used publicly available NCHS mortality data  
139 files for the past 6 influenza seasons to calculate the timing and extent of changes in all-  
140 cause deaths that were explained versus unexplained by changes in reported causes.  
141 The primary research question was whether and to what extent interpretation of the  
142 excess-death metric is potentially vulnerable to unexplained mortality. A secondary  
143 research question was when unexplained deaths occurred relative to specific phases of  
144 the pandemic.

## 145 Methods

146 This study was a retrospective, repeated cross-sectional analysis of U.S.  
147 mortality data. The study outcome was underlying cause of death (UCOD), defined as  
148 “the disease or injury which initiated the train of morbid events leading directly to  
149 death.”<sup>18</sup> Analyses were performed using open-source analytic tools.<sup>8</sup> Data from  
150 October 5, 2014, through September 26, 2020, were downloaded on January 22, 2021;  
151 grouped into 6 influenza seasons, 52 weeks each; and data for the 2014-15 to 2018-19  
152 seasons were population-adjusted to July 2019 using U.S. Census data.<sup>8,19</sup> As in  
153 previous research, Connecticut and North Carolina were excluded because of  
154 incomplete reporting.<sup>6</sup> Data were further grouped *a priori* into time periods roughly  
155 corresponding to U.S. trends in COVID-19 mortality: pandemic awareness (January 19  
156 through March 28); initial pandemic peak (March 29 through May 30); and pandemic  
157 post-peak (May 31 through September 26).<sup>8,20</sup>

158 For each week, time period, and diagnostic category, we calculated prior-season  
159 averages for 3 historical benchmark periods: 2 seasons (2017-18 to 2018-19), 3  
160 seasons (2016-17 to 2018-19), and 5 seasons (2014-15 to 2018-19). For example, the  
161 2-season average for week 1 was the sum of week 1 deaths reported in 2017-18 and  
162 2018-19, divided by 2. Excess deaths were defined *a priori* as increases in all-cause  
163 deaths over these population-adjusted prior-season mean benchmarks. Unexplained  
164 deaths were defined as all-cause deaths not reported in any diagnostic category or  
165 reported as not elsewhere classified (NEC). The decision to parse excess deaths into  
166 explained and unexplained causes was made *post hoc* because large numbers of

unexplained deaths were noticed in analyses for a different exploratory study on cause-of-death attribution.<sup>21</sup>

Results

Of a total of 16.3 million all-cause deaths reported over 6 influenza seasons in 48 states, 2.98 million occurred during 2019-20, representing a population-adjusted increase of 288,467-319,858 excess deaths over prior-season averages for 2, 3, and 5 years (Figure 1, top). Contribution of unexplained mortality to excess deaths varied considerably by pandemic period (Table 1). Of the total increase of 287,957-306,267 all-cause deaths reported from pandemic awareness through end of observation (seasonal weeks 17-52, January 19 through September 26, 2020), 179,903 (58.7%-62.5%) were attributed to COVID-19; 44,022-49,311 (15.2%-16.1%) to changes in reported causes other than COVID-19; 6,909-7,322 (2.3%-2.5%) to increased NEC deaths; and 56,709-70,145 (19.7%-22.9%) to increases in deaths with no reported cause. On a proportional basis, mortality change with unexplained (unreported or NEC) cause was much greater in the pandemic awareness period (65.2%-72.5% of change in all-cause deaths) than in initial pandemic peak or post-peak periods (14.1%-16.1% and 26.6%-29.3%, respectively). In total, an increase of 64,032-77,054 unexplained deaths was responsible for 22.2%-25.2% of change in all-cause mortality from January 19 through September 26, 2020. Increases in explained and unexplained deaths, respectively, began in approximately week 25 (March 15-March in 2020) and week 20 (February 9-February 15 in 2020; Figure 1, bottom).

## Discussion

This analysis of population-adjusted U.S. death certificate data for 6 influenza seasons, the first to assess the extent and timing of unexplained pandemic deaths, indicated substantial impact of unexplained deaths on excess pandemic-period mortality. The most important study limitation is that observation ended on September 26, 2020. Results may not apply to subsequent disease activity, including the surge late in 2020.<sup>20</sup> Additionally, this analysis was descriptive, although it produced results for all-cause deaths similar to those using more sophisticated statistical methods.<sup>6,7</sup>

Despite these limitations, the finding that a large proportion of 2020 mortality was unexplained by changes in top causes of natural death or respiratory disease suggests a need to extend thinking about pandemic mortality beyond COVID-19 or its physical sequelae. Although drug overdoses and suicides are not reported in the available NCHS data, several factors implicate these as potential causes of the unexplained U.S. deaths. These include recent reports of increases in rates of serious psychological distress from 3.9% of adults in 2018 to 13.6% in April 2020<sup>17</sup> and of an 18.2% increase in 12-month overdose death rates from June 2019 to May 2020.<sup>22</sup>

The timing of onset of unexplained deaths suggests they did not result from COVID-19 or sequelae of COVID-19 deaths (e.g., bereavement), but from broader societal factors, particularly early in 2020. Increases in unexplained deaths began about 4-6 weeks before >1,000 COVID-19 cases had been reported nationwide,<sup>20</sup> approximately coinciding with extensive media coverage of COVID-19<sup>23</sup> and a nationwide increase in use of psychotropic medications for anxiety, depression, and sleep disorders.<sup>24</sup> Supporting this interpretation are survey data suggesting no

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significant association between psychological distress and personal acquaintance with someone who died of COVID-19,<sup>25</sup> but strong associations with fear of COVID-19 contagion and of disruption to finances and employment.<sup>15,17</sup>

Expanding pandemic-period mortality research to include societal causes would help to evaluate a concern expressed by the Substance Abuse and Mental Health Services Administration about public health harms caused by focus “solely [on] virus containment” rather than on “all aspects of health.”<sup>26</sup> The addition of a new category for psychiatric UCODs (i.e., International Classification of Disease-10 category F, excluding intellectual and developmental disorders), would facilitate this investigation.

Findings also suggest challenges in interpreting excess death reports because of between-group differences in predispositions to various causes of death.<sup>14,25</sup> For example, the largest percentage increase in U.S. pandemic-period all-cause deaths occurred in adults aged 25-44 years,<sup>7</sup> a group with low rates of COVID-19 mortality but elevated rates of anxiety and mood disorders,<sup>25</sup> suggesting possible underlying psychiatric causes. In contrast, in groups with higher rates of risk factors for COVID-19 mortality, such as obesity or smoking,<sup>4</sup> undetected COVID-19 may be a more likely cause of unexplained all-cause deaths.

Thus, the meaning of an unexplained all-cause excess death may vary across groups or regions. If so, the excess death calculation is uninterpretable when a large proportion of excess deaths is unexplained, highlighting the previously identified urgent need for a more specific and accurate method for certifying mortality from respiratory illness and other causes on death certificates.<sup>3</sup> Quantitative comparisons of mortality outcomes in regions with disparate pandemic policies (e.g., strict stay-at-home orders

versus precautionary warnings), which are essential for evidence-based policy development, cannot be made without accurate and actionable data.

**Conclusion**

Approximately 22%-25% of the increase in all-cause mortality during the U.S. 2020 COVID-19 pandemic was unexplained by changes in the top 8 causes of natural death, COVID-19, sepsis, or other respiratory illness. The onset of unexplained deaths coincided with media coverage and previously reported nationwide increases in psychotropic use. Because unexplained excess deaths may represent disparate underlying causes in different demographic groups or regions, standard excess death calculations may lack utility for evidence-based policy making. Findings highlight the need for improvements in death certification accuracy.

**Funding:** This manuscript was supported solely by Midwestern University and Kathleen Fairman LTD. The research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

**Competing Interests:** Kathleen Fairman is President and James Rucker is Research Intern with Kathleen Fairman LTD, a for-profit research consulting firm. Kathleen Fairman LTD provided analytic support and article processing charges but has no financial or nonfinancial interests related to the topic of the manuscript. Kellie Goodlet and Roy Zawadzki have no competing interests to report.

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**Data Availability Statement**

All source data, analytic packages, and program code for all analyses in this report are publicly available using information and links provided at [https://github.com/JamesRucker/Unexplained\\_deaths](https://github.com/JamesRucker/Unexplained_deaths).

**Author Contributions**

KAF and KJG performed concept and design, assisted by JDR and RSZ. Analyses were performed by KAF and JDR, assisted by RSZ. The manuscript was drafted by KAF and revised for important content by all authors. All authors read and approved of the final manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Patient and Public Involvement**

No patient involved. This study was a retrospective analysis of aggregated death certificate data.

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pandemic. August 14, 2020. [https://www.samhsa.gov/newsroom/press-  
announcements/202008140930](https://www.samhsa.gov/newsroom/press-announcements/202008140930)

For peer review only

Table 1. Overview of Changes in Reported Deaths During Pandemic Periods, 2019-20 Versus Prior-Season Benchmarks

	Total	Explained		Unexplained		
	All Causes	Reported UCOD, COVID-19	Reported UCOD, Not COVID-19 <sup>a</sup>	UCOD Was NEC	Unreported: All-Cause Death, No UCOD <sup>b</sup>	Total <sup>c</sup>
<b>Pandemic awareness period<sup>d</sup></b>						
Prior-season mean, 2-season benchmark	551,845	0	385,438	5,971	160,437	166,408
Prior-season mean, 3-season benchmark	551,951	0	385,863	6,058	160,030	166,088
Prior-season mean, 5-season benchmark	546,260	0	383,245	6,106	156,909	163,015
2019-20	560,736	3,578	384,702	6,577	165,879	172,456
Change, 2-season benchmark	8,891	3,578	-736	606	5,442	6,048
Change, 3-season benchmark	8,785	3,578	-1,161	519	5,849	6,368
Change, 5-season benchmark	14,476	3,578	1,457	471	8,970	9,441
% of change in all-cause deaths, 2-season	100.0%	40.2%	-8.3%	6.8%	61.2%	68.0%
% of change in all-cause deaths, 3-season	100.0%	40.7%	-13.2%	5.9%	66.6%	72.5%
% of change in all-cause deaths, 5-season	100.0%	24.7%	10.1%	3.3%	62.0%	65.2%
<b>Initial pandemic peak period<sup>d</sup></b>						
Prior-season mean, 2-season benchmark	458,044	0	317,107	5,051	135,886	140,937
Prior-season mean, 3-season benchmark	457,300	0	316,944	5,096	135,260	140,356
Prior-season mean, 5-season benchmark	453,618	0	315,900	5,175	132,543	137,718
2019-20	588,710	93,843	335,458	6,061	153,348	159,409
Change, 2-season benchmark	130,666	93,843	18,351	1,010	17,462	18,472
Change, 3-season benchmark	131,410	93,843	18,514	965	18,088	19,053
Change, 5-season benchmark	135,092	93,843	19,558	886	20,805	21,691
% of change in all-cause deaths, 2-season	100.0%	71.8%	14.0%	0.8%	13.4%	14.1%
% of change in all-cause deaths, 3-season	100.0%	71.4%	14.1%	0.7%	13.8%	14.5%
% of change in all-cause deaths, 5-season	100.0%	69.5%	14.5%	0.7%	15.4%	16.1%
<b>Pandemic post-peak<sup>d</sup></b>						
Prior-season mean, 2-season benchmark	829,780	0	567,619	9,639	252,522	262,161
Prior-season mean, 3-season benchmark	827,727	0	567,244	9,634	250,850	260,484
Prior-season mean, 5-season benchmark	821,482	0	565,731	9,793	245,958	255,751
2019-20	978,181	82,482	594,026	15,345	286,328	301,673
Change, 2-season benchmark	148,401	82,482	26,407	5,706	33,806	39,512
Change, 3-season benchmark	150,454	82,482	26,782	5,711	35,478	41,189
Change, 5-season benchmark	156,699	82,482	28,295	5,552	40,370	45,922
% of change in all-cause deaths, 2-season	100.0%	55.6%	17.8%	3.8%	22.8%	26.6%
% of change in all-cause deaths, 3-season	100.0%	54.8%	17.8%	3.8%	23.6%	27.4%
% of change in all-cause deaths, 5-season	100.0%	52.6%	18.1%	3.5%	25.8%	29.3%
<b>Total changes, pandemic awareness through end of observation</b>						
2-season benchmark	287,957	179,903	44,022	7,322	56,709	64,032
% of change in all-cause deaths, 2-season	100.0%	62.5%	15.3%	2.5%	19.7%	22.2%
3-season benchmark	290,649	179,903	44,136	7,195	59,415	66,610
% of change in all-cause deaths, 3-season	100.0%	61.9%	15.2%	2.5%	20.4%	22.9%
5-season benchmark	306,267	179,903	49,311	6,909	70,145	77,054
% of change in all-cause deaths, 5-season	100.0%	58.7%	16.1%	2.3%	22.9%	25.2%

<sup>a</sup> Sum of specific causes other than COVID-19 reported in the mortality files, including heart disease, cancer, chronic lower respiratory disease, cerebrovascular disease, Alzheimer's disease, diabetes, influenza-pneumonia, other respiratory illness, kidney disease, and septicemia. Diagnosis codes for each category are in Supplement Appendix 1. <sup>b</sup> All-cause deaths not reported in any of the categories of death included in the mortality files, including those listed in footnote <sup>a</sup>, NEC deaths, or COVID-19. <sup>c</sup> NEC deaths plus unreported deaths. <sup>d</sup> Pandemic awareness is from weeks 17-26 (January 19 through March 28 in 2019-20 season). Initial pandemic peak is from weeks 27-35 (March 29 through May 30 in 2019-20 season). Pandemic post-peak is from weeks 36-52 (May 31 through September 26 in 2019-20 season). COVID-19=coronavirus-19; NEC=not elsewhere classified; UCOD=underlying cause of death.

Figure 1 Legend

Figure 1. Trends in Population-Adjusted Death Counts by Week of Influenza Season,<sup>a</sup>  
2014-15 Through 2019-20 Seasons

<sup>a</sup> For each influenza season, week 1 begins on approximately October 1 and week 52 ends on approximately September 30. A total of 312 weeks (52 weeks for 6 seasons) were included in the analyses. Prior-season benchmarks are means (deaths summed across seasons, divided by 2, 3, and 5, respectively, for 2-season, 3-season, and 5-season benchmarks). <sup>b</sup> Explained deaths include specific causes reported in the mortality files, including heart disease, cancer, chronic lower respiratory disease, cerebrovascular disease, Alzheimer's disease, diabetes, influenza-pneumonia, other respiratory illness, kidney disease, septicemia, and COVID-19. Diagnosis codes for each category are in Supplement Appendix 1. Unexplained deaths are all-cause deaths with no reported underlying cause or with a not elsewhere classified cause (all-cause deaths minus explained deaths). COVID-19=coronavirus-19.

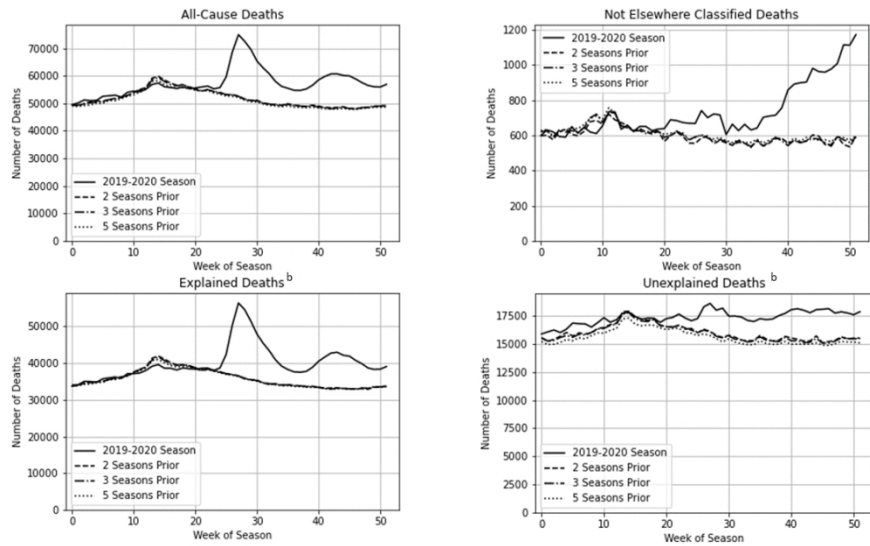


Figure 1. Trends in Population-Adjusted Death Counts by Week of Influenza Season,a 2014-15 through 2019-20 Seasons

a For each influenza season, week 1 begins on approximately October 1, and week 52 ends on approximately September 30. A total of 312 weeks (52 weeks for 6 seasons) were included in the analyses. Prior-season benchmarks are means (deaths summed across seasons, divided by 2, 3, and 5, respectively, for 2-season, 3-season, and 5-season benchmarks). b Explained deaths include specific causes reported in the mortality files, including heart disease, cancer, chronic lower respiratory disease, cerebrovascular disease, Alzheimer's disease, diabetes, influenza-pneumonia, other respiratory illness, kidney disease, septicemia, and COVID-19. Diagnosis codes for each category are in Appendix 1. Unexplained deaths are all-cause deaths with no reported underlying cause or with a not elsewhere classified cause (all-cause deaths minus explained deaths). COVID-19=coronavirus-19.

1 Appendix 1. ICD-10 Category Descriptions in NCHS Files, Ranked in Descending Order  
 2 by U.S. Death Counts in 2017<sup>8</sup>

<b>NCHS Category: Diseases of the Heart (I00-I09; I11 I13; I20-I51)</b>	
I00-I02 Acute rheumatic fever	
I05-I09 Chronic rheumatic heart diseases;	
I11 Hypertensive heart disease	
I13 Hypertensive heart and chronic kidney disease	
I20 Angina pectoris	
I21 Acute myocardial infarction	
I22 Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction	
I23 Certain complications following ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction (within the 28 day period)	
I24 Other acute ischemic heart diseases	
I25 Chronic ischemic heart disease	
I26-I28 Pulmonary heart disease and diseases of pulmonary circulation	
I30 Acute pericarditis	
I31 Other diseases of pericardium	
I32 Pericarditis in diseases classified elsewhere	
I33 Acute and subacute endocarditis	
I34 Nonrheumatic mitral valve disorders	
I35 Nonrheumatic aortic valve disorders	
I36 Nonrheumatic tricuspid valve disorders	
I37 Nonrheumatic pulmonary valve disorders	
I38 Endocarditis, valve unspecified	
I39 Endocarditis and heart valve disorders in diseases classified elsewhere	
I40 Acute myocarditis	
I41 Myocarditis in diseases classified elsewhere	
I42 Cardiomyopathy	
I43 Cardiomyopathy in diseases classified elsewhere	
I44 Atrioventricular and left bundle-branch block	
I45 Other conduction disorders	
I46 Cardiac arrest	
I47 Paroxysmal tachycardia	
I48 Atrial fibrillation and flutter	
I49 Other cardiac arrhythmias	
I50 Heart failure	
I51 Complications and ill-defined descriptions of heart disease	
<b>NCHS Category: Malignant Neoplasms (C00-C97)</b>	
Code range includes malignant neoplasms of all types	
<b>NCHS Category: Chronic Lower Respiratory Disease (J40-J47)</b>	
J40 Bronchitis, not specified as acute or chronic	
J41 Simple and mucopurulent chronic bronchitis	
J42 Unspecified chronic bronchitis	
J43 Emphysema	
J44 Other chronic obstructive pulmonary disease	
J45 Asthma	
J46 Status asthmaticus	
J47 Bronchiectasis	
<b>NCHS Category: Cerebrovascular Disease (I60-I69)</b>	
I60 Nontraumatic subarachnoid hemorrhage	
I61 Nontraumatic intracerebral hemorrhage	
I62 Other and unspecified nontraumatic intracranial hemorrhage	
I63 Cerebral infarction	
I64 Stroke, not specified if hemorrhagic or infarct	

I65	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction
I66	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction
I67	Other cerebrovascular diseases
I68	Cerebrovascular disorders in diseases classified elsewhere
I69	Sequelae of cerebrovascular disease
<b>NCHS Category: Alzheimer's Disease (G30)</b>	
G30	Alzheimer's disease
<b>NCHS Category: Diabetes (E10-E14)</b>	
E10	Type 1 diabetes mellitus
E11	Type 2 diabetes mellitus
E13	Other specified diabetes mellitus
E14	is an old code for unspecified diabetes mellitus
<b>NCHS Category: Influenza and Pneumonia (J10-J18)</b>	
J10	Influenza due to other identified influenza virus
J11	Influenza due to unidentified influenza virus
J12	Viral pneumonia, not elsewhere classified
J13	Pneumonia due to Streptococcus pneumoniae
J14	Pneumonia due to Hemophilus influenzae
J15	Bacterial pneumonia, not elsewhere classified
J16	Pneumonia due to other infectious organisms, not elsewhere classified
J17	Pneumonia in diseases classified elsewhere
J18	Pneumonia, unspecified organism
<b>NCHS Category: Nephritis, Nephrotic Syndrome, and Nephrosis (N00-N07, N17-N19, N25-N27)</b>	
N00	Acute nephritic syndrome
N01	Rapidly progressive nephritic syndrome
N02	Recurrent and persistent hematuria
N03	Chronic nephritic syndrome
N04	Nephrotic syndrome
N05	Unspecified nephritic syndrome
N06	Isolated proteinuria with specified morphological lesion
N07	Hereditary nephropathy, not elsewhere classified
N17	Acute kidney failure
N18	Chronic kidney disease
N19	Unspecified kidney failure
N25	Disorders resulting from impaired renal tubular function
N26	Unspecified contracted kidney
N27	Small kidney of unknown cause
<b>NCHS Category: Other Diseases of the Respiratory System (J00-J06,J30-J39,J67,J70-J98)</b>	
J00	Acute nasopharyngitis [common cold]
J01	Acute sinusitis
J02	Acute pharyngitis
J03	Acute tonsillitis
J04	Acute laryngitis and tracheitis
J05	Acute obstructive laryngitis [croup] and epiglottitis
J06	Acute upper respiratory infections of multiple and unspecified sites
J30	Vasomotor and allergic rhinitis
J31	Chronic rhinitis, nasopharyngitis and pharyngitis
J32	Chronic sinusitis
J33	Nasal polyp
J34	Other and unspecified disorders of nose and nasal sinuses
J35	Chronic diseases of tonsils and adenoids
J36	Peritonsillar abscess
J37	Chronic laryngitis and laryngotracheitis
J38	Diseases of vocal cords and larynx, not elsewhere classified
J39	Other diseases of upper respiratory tract

J67 Hypersensitivity pneumonitis due to organic dust  
 J70 Respiratory conditions due to other external agents  
 J80 Acute respiratory distress syndrome  
 J81 Pulmonary edema  
 J82 Pulmonary eosinophilia, not elsewhere classified  
 J84 Other interstitial pulmonary diseases  
 J85 Abscess of lung and mediastinum  
 J86 Pyothorax  
 J90 Pleural effusion, not elsewhere classified  
 J91 Pleural effusion in conditions classified elsewhere  
 J92 Pleural plaque  
 J93 Pneumothorax and air leak  
 J94 Other pleural conditions  
 J95-J95 Intraoperative and postprocedural complications and disorders of respiratory system, not elsewhere classified  
 J96 Respiratory failure, not elsewhere classified  
 J98 Other respiratory disorders

**NCHS Category: Septicemia (A40-A41)**

A40 Streptococcal sepsis  
 A41 Other sepsis

**NCHS Category: Symptoms, Signs, and Abnormal Clinical and Laboratory Findings (R00-R99)**

R00-R09 Symptoms and signs involving the circulatory and respiratory systems  
 R10-R19 Symptoms and signs involving the digestive system and abdomen  
 R20-R23 Symptoms and signs involving the skin and subcutaneous tissue  
 R25-R29 Symptoms and signs involving the nervous and musculoskeletal systems  
 R30-R39 Symptoms and signs involving the genitourinary system  
 R40-R46 Symptoms and signs involving cognition, perception, emotional state and behavior  
 R47-R49 Symptoms and signs involving speech and voice  
 R50-R69 General symptoms and signs  
 R70-R79 Abnormal findings on examination of blood, without diagnosis  
 R80-R82 Abnormal findings on examination of urine, without diagnosis  
 R83-R89 Abnormal findings on examination of other body fluids, substances and tissues, without diagnosis  
 R90-R94 Abnormal findings on diagnostic imaging and in function studies, without diagnosis  
 R97-R97 Abnormal tumor markers  
 R99-R99 Ill-defined and unknown cause of mortality

ICD=International Classification of Diseases codes available at <https://www.icd10data.com/>; NCHS=National Center for Health Statistics

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	Retrospective analysis--title, page 1  Abstract, page 3	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included.  RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract.  RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Type of data: death certificates--title, page 1  Name of database--abstract, page 2  Region--U.S., title, page 1  Timeframe--abstract, page 2
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Pages 5-6		
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 6, last paragraph of introduction		
Methods					
Study Design	4	Present key elements of study design early in the paper	Title, page 1 Abstract, page 2 First paragraph of methods, page 7		
Setting	5	Describe the setting, locations, and relevant dates, including	Page 7		

		periods of recruitment, exposure, follow-up, and data collection			
Participants	6	<p>(a) <i>Cohort study</i> - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up</p> <p><i>Case-control study</i> - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls</p> <p><i>Cross-sectional study</i> - Give the eligibility criteria, and the sources and methods of selection of participants</p> <p>(b) <i>Cohort study</i> - For matched studies, give matching criteria and number of exposed and unexposed</p> <p><i>Case-control study</i> - For matched studies, give matching criteria and the number of controls per case</p>	Page 7	<p>RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided.</p> <p>RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided.</p> <p>RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.</p>	<p>Appendix 1</p> <p>Inapplicable, but previous uses of database are described on page 5</p> <p>Inapplicable—no linkage</p>
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	<p>Outcome—page 7</p> <p>Diagnosis codes—Appendix 1</p>	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Appendix 1
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement).	Pages 7-8		

		Describe comparability of assessment methods if there is more than one group	Inapplicable—one population group		
Bias	9	Describe any efforts to address potential sources of bias	Inapplicable—descriptive analysis of single population		
Study size	10	Explain how the study size was arrived at	Inapplicable—population		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Page 7		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) <i>Cohort study</i> - If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> - If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	Page 7  Inapplicable  Inapplicable  Inapplicable		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database	Page 7 – data are publicly available online

				population used to create the study population.	
				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	Inapplicable
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Inapplicable—no linkages
<b>Results</b>					
Participants	13	(a) Report the numbers of individuals at each stage of the study ( <i>e.g.</i> , numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		RECORD 13.1: Describe in detail the selection of the persons included in the study ( <i>i.e.</i> , study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Inapplicable—100% of deaths in 48 states, page 6
Descriptive data	14	(a) Give characteristics of study participants ( <i>e.g.</i> , demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) <i>Cohort study</i> - summarise follow-up time ( <i>e.g.</i> , average and total amount)	First paragraph of Results, page 8  Inapplicable—unreported (missing) cause of death is the topic of the study		

Outcome data	15	<i>Cohort study</i> - Report numbers of outcome events or summary measures over time <i>Case-control study</i> - Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> - Report numbers of outcome events or summary measures	Page 7		
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	All estimates are unadjusted; population data, CIs inapplicable  Inapplicable		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Inapplicable		
<b>Discussion</b>					
Key results	18	Summarise key results with reference to study objectives	Page 9, first paragraph of Discussion		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 9, first paragraph of Discussion	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing	Classification and changes over time were topics of the study

				data, and changing eligibility over time, as they pertain to the study being reported.	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Pages 9-10		
Generalisability	21	Discuss the generalisability (external validity) of the study results	Inapplicable—population data		
<b>Other Information</b>					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	No external funding but work was supported by authors' employers—page 11		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Reference #8, page 14, link to Github site with all data and code

\*Reference: Benchimol EI, Smeeth L, Guttman A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

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# BMJ Open

## Unexplained Mortality During the U.S. COVID-19 Pandemic: Retrospective Analysis of Death Certificate Data and Critical Assessment of Excess Death Calculations

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-050361.R1
Article Type:	Original research
Date Submitted by the Author:	14-Jul-2021
Complete List of Authors:	Fairman, Kathleen; Midwestern University College of Pharmacy - Glendale, Department of Pharmacy Practice; Kathleen Fairman LTD Goodlet, Kellie; Midwestern University College of Pharmacy - Glendale, Department of Pharmacy Practice Rucker, James; Kathleen Fairman LTD Zawadzki, Roy; University of California Irvine
<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Public health, Mental health
Keywords:	COVID-19, EPIDEMIOLOGY, MENTAL HEALTH, PUBLIC HEALTH, STATISTICS & RESEARCH METHODS, Health informatics < BIOTECHNOLOGY & BIOINFORMATICS

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Unexplained Mortality During the U.S. COVID-19 Pandemic:  
Retrospective Analysis of Death Certificate Data and Critical Assessment of  
Excess Death Calculations

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Word count: 2844   Tables: 1   Figures: 1   Appendix: 2

Keywords: COVID-19, mortality, death certification, epidemiological methods, mental health

Abstract

Objectives: Cause-of-death discrepancies are common in respiratory illness-related mortality. A standard epidemiological metric, excess all-cause death, is unaffected by these discrepancies but provides no actionable policy information when increased all-cause mortality is unexplained by reported specific causes. To assess the contribution of unexplained mortality to the excess-death metric, we parsed excess deaths in the coronavirus-2019 (COVID-19) pandemic into changes in explained versus unexplained (unreported or unspecified) causes.

Design: Retrospective repeated cross-sectional analysis, U.S. death-certificate data for 6 influenza seasons beginning October 2014, comparing population-adjusted historical benchmarks from the previous 2, 3, and 5 seasons with 2019-20.

Setting: 48 of 50 states with complete data.

Participants: 16.3 million deaths in 312 weeks, reported in categories—all causes, top 8 natural causes, and respiratory causes including COVID-19.

Outcome Measures: Change in population-adjusted counts of deaths from seasonal benchmarks to 2019-20, from all causes (i.e., total excess deaths) and from explained versus unexplained causes, reported for the season overall and for time periods defined *a priori*: pandemic awareness (January 19 through March 28); initial pandemic peak (March 29 through May 30); and pandemic post-peak (May 31 through September 26).

Results: Depending on seasonal benchmark, 287,957-306,267 excess deaths occurred through September 2020: 179,903 (58.7%-62.5%) attributed to COVID-19; 44,022-49,311 (15.2%-16.1%) to other reported causes; 64,032-77,054 (22.2%-25.2%) unexplained (unspecified or unreported cause). Unexplained deaths constituted 65.2%-

72.5% of excess deaths from January 19 to March 28 and 14.1%-16.1% from March 29 through May 30.

Conclusions: Unexplained mortality contributed substantially to U.S. pandemic-period excess deaths. Onset of unexplained mortality in February 2020 coincided with previously reported increases in psychotropic use, suggesting possible psychiatric or injurious causes. Because underlying causes of unexplained deaths may vary by group or region, results suggest excess death calculations provide limited actionable information, supporting previous calls for improved cause-of-death data to support evidence-based policy.

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**Strengths and limitations of this study**

This is the first study to assess the degree to which mortality from unreported or unspecified causes contributed to excess deaths in the U.S. coronavirus-19 pandemic, raising important policy questions about the utility of the excess-death metric.

We used population-adjusted U.S. national data, accounting for deaths in every category reported by the National Center for Health Statistics (NCHS), including top natural causes and respiratory causes including COVID-19.

Our statistical analysis was descriptive, but our estimates of excess deaths are similar to those previously developed using more sophisticated statistical analyses of the same data files.

Study results generalize to the United States through September 26, 2020, but not to other countries, as cause-of-death attribution practices vary cross-nationally, or to other pandemic periods, including the COVID-19 case surge in late 2020.

Although we cite evidence suggesting many of the unspecified-cause deaths may have been due to suicide, overdose, or underlying psychiatric causes, we were unable to address this question using the available NCHS data files, particularly in population subgroups that may have been especially vulnerable to injurious causes of mortality during the pandemic.

## 101 Introduction

102 Errors in cause-of-death attribution (CODA) are common in infectious respiratory  
103 illness, compromising accurate tracking of disease impact and spread.<sup>1-3</sup> CODA is  
104 especially challenging in coronavirus disease 2019 (COVID-19) because of competing  
105 causes of mortality, including cancer, lung disease, obesity-related conditions, and  
106 superannuation.<sup>4</sup> Compounding this problem, key factors contributing to COVID-19  
107 CODA, such as level of training and expertise of mortality coders, whether laboratory  
108 testing is or is not required, financial incentives for reporting, and public health delivery  
109 systems, vary considerably by country.<sup>5,6</sup> These variations make cross-national  
110 comparisons of COVID-19-attributed mortality problematic, threatening the accuracy of  
111 the virus mortality statistics needed for public health decision making.<sup>3</sup>

112 A standard metric generally understood to account for these discrepancies is  
113 “excess death,” defined as mortality from all causes exceeding that expected from  
114 historical experience.<sup>7</sup> Recent investigators have calculated excess deaths to estimate  
115 U.S. COVID-19 impact, using death certificate data made available by the U.S. National  
116 Center for Health Statistics (NCHS).<sup>7-9</sup> Most interpretations of excess death calculations  
117 reflect an underlying assumption that 100% of the change in mortality that took place  
118 during the pandemic was attributable, indirectly or directly, to COVID-19.<sup>7,8,10</sup> The  
119 calculation has the advantages of no reliance on CODA, because it considers only all-  
120 cause deaths, and of accounting for deaths due to undetected COVID-19 or to use of  
121 scarce health system resources by infected patients.<sup>7,8,10</sup>

122 Despite these advantages, the utility and interpretation of excess death  
123 calculations may be compromised by unexplained deaths. Fully adjudicated, final U.S.

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mortality files report specific causes or contributing factors, as well as demographic characteristics, for each individual decedent.<sup>11,12</sup> In contrast, files made available by the NCHS beginning in May 2020 to facilitate pandemic-mortality analysis, which have been used to calculate excess deaths as an indication of the “full COVID-19 burden,”<sup>8</sup> report only aggregated (summed) weekly death counts, grouped into broad diagnostic categories.<sup>13,14</sup> These categories, shown in Supplement Appendix 1, represent ranges of International Classification of Diseases, Tenth Revision (ICD-10) diagnosis codes.<sup>13,14</sup> For excess deaths unexplained by these causes, the true underlying causes are unknown, despite presumably representing appropriate policy targets. For example, markedly different interventions would be suggested by unexplained deaths due to undetected COVID-19, high-speed automobile accidents on empty highways,<sup>15</sup> or delayed care for life-threatening conditions when people fear using available emergency department capacity.<sup>16</sup>

Risk factors for potential causes of unexplained death vary cross-nationally. For example, U.S. opioid supplies, opioid mortality, substance use disorder prevalence, and suicide rates far exceed those of other high-income nations,<sup>17</sup> suggesting greater psychological vulnerability to pandemic-period disruptions. Yet, neither substance misuse nor mental illness is recorded as a cause of death in the currently available NCHS pandemic period mortality files.<sup>13,14</sup> Risk factors for COVID-19 mortality, such as obesity, smoking, and healthcare associated infections, also demonstrate considerable cross-national variability.<sup>17</sup>

Quantifying unexplained excess deaths would provide information about the degree to which the utility and interpretation of excess death calculations are potentially

compromised by unreported or unspecified causes of mortality. Moreover, assessing the timing of unexplained deaths at various pandemic phases would inform current discussions about societal factors that may contribute to pandemic-period morbidity and mortality, such as fear of contagion or economic vulnerability.<sup>18-20</sup> Accordingly, we used publicly available NCHS mortality data files for the past 6 influenza seasons to calculate the timing and extent of changes in all-cause deaths that were explained versus unexplained by changes in reported causes.

The primary research question was to what degree unexplained mortality contributed to excess mortality during the pandemic. Because the excess mortality calculation represents change in mortality compared with historical experience, we addressed this research question by assessing the contributions of changes in explained versus unexplained causes of death to change in total, all-cause death. A secondary research question, formed to explore possible reasons for unexplained mortality, was when unexplained deaths escalated in 2020.

## Methods

### *Design and Data Source*

This study was a retrospective, repeated cross-sectional analysis of U.S. mortality files made available by the NCHS beginning in 2020 for pandemic-period analysis. The data files for 2020 represent provisional causes of death.<sup>13</sup> The corresponding data files for 2014-2019 represent final adjudicated causes of death,<sup>14</sup> reported in the same broad diagnostic categories as the 2020 data to facilitate analysis (Supplement Appendix 1).

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The study measures were based on reported underlying cause of death (UCOD), defined as “the disease or injury which initiated the train of morbid events leading directly to death.”<sup>21</sup> Only one UCOD is reported on each death certificate. The study files include weekly counts of deaths in total (all-cause) and by UCOD category, grouped by state.

In addition to categories representing the top 8 U.S. causes of natural death (heart disease, cancer, chronic lower respiratory disease, cerebrovascular disease, Alzheimer’s disease, diabetes, influenza and pneumonia, and kidney disease), which together accounted for 66% of all U.S. deaths in 2017,<sup>22</sup> the files include four additional categories: miscellaneous respiratory conditions, (e.g., nasopharyngitis, sinusitis, pneumothorax); septicemia; COVID-19; and nonspecific-cause deaths.<sup>13,14</sup> These deaths, described in ICD-10 nomenclature as “symptoms, signs, and abnormal clinical and laboratory findings not elsewhere classified” (NEC; ICD-10 range R00-R99), include “ill-defined and unknown cause of mortality” (R99),<sup>13,14</sup> a code commonly used pending forensic investigation of injurious death.<sup>23</sup> Neither the 2020 provisional data nor the corresponding grouped data for 2014-2019 include reporting categories for specific psychiatric causes, including substance use disorders (ICD-10 codes F00-F99 excluding developmental disorders), or for injurious deaths including intentional self-harm (ICD-10 codes X71-X83) and unintentional overdose (ICD-10 codes T36-T50, excluding codes for underdosing).<sup>24</sup>

*Data Analyses*

Data from October 5, 2014, through September 26, 2020, were downloaded on January 22, 2021. Analyses were performed using open-source analytic tools.<sup>11</sup>

Specifically, Python coding was used with Pandas, a data-organization tool,<sup>25,26</sup> to group data into 6 influenza seasons, 52 weeks each. Using the same software tools, data for the 2014-15 to 2018-19 seasons were population-adjusted to July 2019 using U.S. Census data.<sup>11,27</sup> As in previous research, Connecticut and North Carolina were excluded because of incomplete reporting.<sup>8</sup> Data were further grouped *a priori* into time periods roughly corresponding to U.S. trends in COVID-19 mortality: pandemic awareness (January 19 through March 28); initial pandemic peak (March 29 through May 30); and pandemic post-peak (May 31 through September 26).<sup>11,28</sup>

Analyses were descriptive to facilitate the parsing of excess death (i.e., change in all-cause death) into explained and unexplained proportions. The decision was in accordance with the principle of parsimony in data presentation,<sup>29</sup> as we found that descriptive results were similar to those produced using more sophisticated techniques.<sup>8,9</sup> For each week, time period, and diagnostic category, we calculated prior-season averages for 3 historical benchmark periods: 2 seasons (2017-18 to 2018-19), 3 seasons (2016-17 to 2018-19), and 5 seasons (2014-15 to 2018-19). Averages were calculated as total death count for the indicated time period, divided by number of years. For example, the 2-season average for week 1 was the sum of week 1 deaths reported in 2017-18 and 2018-19, divided by 2. Three benchmark time periods were used because it is common to compare current-year mortality data with several historical benchmarks,<sup>30</sup> consistent with the need to report sensitivity analyses of epidemiological data.<sup>31</sup> Weekly prior-season averages and 2019-20 counts were graphed using Matplotlib.<sup>32</sup>

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For each week and time period, excess deaths were defined *a priori* as increases in all-cause deaths over the population-adjusted prior-season mean benchmarks (i.e., 2019-20 season values minus benchmark values). Unexplained deaths were defined as all-cause deaths either not reported in any diagnostic category (unreported) or reported in the NEC category (unspecified). Explained deaths were defined as all-cause deaths reported in any of the specific cause-of-death categories (i.e., all-cause minus unexplained deaths). The decision to parse excess deaths into explained and unexplained causes was made *post hoc* because large numbers of unexplained deaths were noticed in analyses for a different exploratory study on cause-of-death attribution.<sup>33</sup> Changes in explained and unexplained causes were calculated using the same method as for excess deaths, by first calculating the population-adjusted prior-season mean benchmarks, then subtracting the benchmark values from the 2019-20 season values.

Results

Of a total of 16.3 million all-cause deaths reported over 6 influenza seasons in 48 states, 2.98 million occurred during 2019-20, representing a population-adjusted increase of 288,467-319,858 excess deaths over prior-season averages for 2, 3, and 5 years (Figure 1, top). Mean annual population-adjusted total all-cause death counts varied modestly across seasonal benchmarks, ranging from 2,659,228 to 2,690,619. An increase in NEC deaths began in approximately week 19 and escalated sharply beginning at week 36 (May 31 in the 2019-20 season) through end of observation. Increases in explained and unexplained deaths, respectively, began in approximately

week 25 (March 15-March in 2020) and week 20 (February 9-February 15 in 2020; Figure 1, bottom).

Contribution of unexplained mortality to excess deaths varied considerably by pandemic period (Table 1). Using the 5-year benchmark, of the total increase of 306,267 all-cause deaths reported from pandemic awareness through end of observation (seasonal weeks 17-52, January 19 through September 26, 2020), 179,903 (58.7%) were attributed to COVID-19; 49,311 (16.1%) to changes in reported causes other than COVID-19; 6,909 (2.3%) to increased NEC deaths; and 70,145 (22.9%) to increases in deaths with no reported cause. On a proportional basis, mortality change with unexplained (unreported or NEC) cause was much greater in the pandemic awareness period (January 19 through March 28, 65.2% of change in all-cause deaths) than in the initial pandemic peak period (March 29 through May 30, 16.1%) or the post-peak period (May 31 through September 26, 29.3%). In total, an increase of 77,054 unexplained deaths was responsible for 25.2% of change in all-cause mortality from January 19 through September 26, 2020.

Results using the 2- and 3-year benchmarks were similar (Supplement Appendix 2). Using these benchmarks, increases in unexplained deaths accounted for 68.0%-72.5% of excess deaths during the pandemic awareness period; 14.1%-14.5% of excess deaths during initial peak; and 26.6%-27.4% of excess deaths in the pandemic post-peak period. Measured from pandemic awareness through the end of observation, changes in unexplained deaths accounted for 22.2%-22.9% of excess deaths.

## Discussion

This analysis of population-adjusted U.S. death certificate data for 6 influenza seasons, the first to assess the extent and timing of unexplained pandemic deaths,

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indicated substantial impact of unexplained deaths on excess pandemic-period mortality. The most important study limitation is that observation ended on September 26, 2020. Results may not apply to subsequent disease activity, including the surge late in 2020.<sup>28</sup> Additionally, this analysis was descriptive, although it produced results for all-cause deaths similar to those using more sophisticated statistical methods.<sup>8,9</sup> For example, the 299,028 excess deaths estimated by the CDC using Poisson regression modeling through October 3, 2020<sup>9</sup> is comparable to our estimate of 287,957-306,267 excess deaths through September 26, 2020.

Despite these limitations, the finding that a large proportion of 2020 excess mortality was unexplained by changes in top causes of natural death or respiratory disease suggests a need to extend thinking about pandemic mortality beyond COVID-19 or its physical sequelae. Although drug overdoses and suicides are not reported in the available NCHS data, several factors implicate these as potential causes of the unexplained U.S. deaths. These include reports of increases in rates of serious psychological distress from 3.9% of adults in 2018 to 13.6% in April 2020<sup>20</sup> and of an 18.2% increase in 12-month overdose death rates from June 2019 to May 2020.<sup>34</sup> The increase in NEC deaths, which accelerated sharply beginning in approximately May 2020, is also consistent with this explanation because the R99 category included in the ICD-10 NEC group is commonly used pending forensic investigation of injurious death, introducing a lag period before cause-of-death determination.<sup>23</sup> However, the NEC increases could also represent COVID-19 not yet diagnosed because of pending laboratory testing.

282 Countering suicides but supporting overdose as causal factors underlying the  
283 unexplained deaths, recently released U.S. mortality data reported through August 2020  
284 suggested early pandemic-period increases in overdoses, homicides, and unintentional  
285 injuries, but decreases in suicides and motor vehicle accidents, relative to historical  
286 experience.<sup>35</sup> An important caveat to these early findings is that they represent the U.S.  
287 as a whole, possibly masking outcomes in economically and socially vulnerable  
288 populations that were already at increased risk of behavioral health-related mortality  
289 prior to the pandemic.<sup>36-39</sup> Among these are young adults, described in a U.S.  
290 Substance Abuse and Mental Health Services (SAMHSA) report as “a uniquely  
291 vulnerable population” based on pandemic-period data on anxiety, depression,  
292 traumatic stress, psychological distress, loneliness, substance misuse, and suicidal  
293 ideation.<sup>37</sup> Also at elevated risk were women, racial and ethnic minorities, health care  
294 workers, and pediatric populations.<sup>36-39</sup> These disparate behavioral health effects  
295 suggest that the underlying causes of excess deaths should be explored in U.S.  
296 population subgroups, rather than only for the nation as a whole.

297 Also supporting the interpretation of possible behavioral health effects, the timing  
298 of onset of unexplained deaths in February 2020 suggests they did not result from  
299 COVID-19 or sequelae of COVID-19 deaths (e.g., bereavement). Increases in  
300 unexplained deaths began about 4-6 weeks before >1,000 COVID-19 cases had been  
301 reported nationwide,<sup>28</sup> approximately coinciding with extensive media coverage of  
302 COVID-19<sup>40</sup> and a nationwide increase in use of psychotropic medications for anxiety,  
303 depression, and sleep disorders.<sup>41</sup> Also supporting this interpretation are survey data  
304 suggesting no significant association between psychological distress and personal

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acquaintance with someone who died of COVID-19,<sup>42</sup> but strong associations with fear of COVID-19 contagion and of disruption to finances and employment.<sup>18,20</sup>

Moreover, a content analysis of media coverage of the pandemic, posted as a nonpeer-reviewed working paper in November 2020, found that 91% of U.S. major media stories, compared with 54% of non-U.S. stories and 65% of scientific journal reports, were “negative in tone.”<sup>43</sup> These preliminary findings suggest a possible bias unique to U.S. media coverage of COVID-19. If confirmed with peer-reviewed research, the connection between this bias and psychological distress should be explored in additional studies. Neither the psychological effects of media coverage nor the specific causes of the unexplained deaths we observed could be assessed with available provisional mortality data. However, release of the full, final U.S. cause-of-death file for 2020, which likely will occur by early 2022, will make analyses of psychiatric and injurious causes of death, overall and by demographic and regional subgroups, feasible.

Expanding pandemic-period mortality research to include societal causes would help to evaluate a concern expressed by the Substance Abuse and Mental Health Services Administration about public health harms caused by focus “solely [on] virus containment” rather than on “all aspects of health.”<sup>44</sup> The addition of new UCOD categories for behavioral disorders, including psychiatric and substance use disorders, intentional self-harm, and unintentional overdose, to the available files would facilitate this investigation. Together, these causes accounted for approximately 106,000 U.S. deaths per year from 2010-2018,<sup>45</sup> and their prevalence as UCODs has increased rapidly over time.<sup>46-47</sup> The provisional files released by the NCHS in March of 2021, which included the diagnostic categories assessed in this research plus categories for

accidents, intentional self-harm, homicide, and drug overdoses,<sup>48</sup> were aggregated monthly for the U.S. as a whole and therefore do not facilitate comparative policy analysis, such as by states with varying pandemic policies (e.g., strict stay-at-home orders versus precautionary warnings).

Findings also suggest challenges in interpreting excess death reports because of between-group differences in predispositions to various causes of death.<sup>17,42</sup> For example, the largest percentage increase in U.S. pandemic-period all-cause deaths occurred in adults aged 25-44 years,<sup>9</sup> a group with low rates of COVID-19 mortality but elevated rates of anxiety and mood disorders,<sup>42</sup> suggesting possible underlying psychiatric causes. Similarly, the U.S. had the fourth-highest rate of alcohol dependence (8%) and the highest rate of opioid-related deaths (131 per million) in the world in 2016,<sup>17</sup> implicating substance-related mortality as a likely contributor to unexplained deaths. In contrast, in groups with higher rates of risk factors for COVID-19 mortality, such as obesity or smoking,<sup>4</sup> undetected COVID-19 may be a more likely cause of unexplained all-cause deaths. For example, rates of adult (aged  $\geq 15$  years) smoking in 2017 ranged from 10% or less in the U.S. and other countries (e.g., Mexico, 8%) to  $\geq 25\%$  in France, Hungary, Turkey, Greece, Russia, and Indonesia.<sup>17</sup> Similarly, within the U.S., statewide rates of obesity among adults in 2019 ranged from 24% to 41%.<sup>49</sup>

These large risk factor variations across groups and regions could represent markedly disparate true underlying causes for unexplained all-cause deaths. If so, the excess death calculation is uninterpretable when a large proportion of excess deaths is unexplained. This problem, which affected 22%-25% of the excess pandemic-period

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3 351 deaths measured through September 2020, suggests that excess death calculations do  
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5 352 not consistently provide actionable information and highlights previous calls for specific,  
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7 353 standardized algorithms to certify mortality from respiratory illness and other causes on  
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10 354 death certificates.<sup>1,3</sup>  
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12 355 Conclusion  
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14 356 Approximately 22%-25% of the increase in all-cause mortality during the U.S. 2020  
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16 357 COVID-19 pandemic was unexplained by changes in the top 8 causes of natural death,  
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18 358 COVID-19, sepsis, or other respiratory illness. The onset of unexplained deaths  
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22 360 psychotropic use. Because unexplained excess deaths may represent disparate  
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24 361 underlying causes in different demographic groups or regions, standard excess death  
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26 362 calculations may lack utility for evidence-based policy making. Findings highlight the  
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28 363 need for improvements in death certification accuracy.  
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35 365 **Funding:** This manuscript was supported solely by Midwestern University and Kathleen  
36  
37 366 Fairman LTD. The research received no specific grant from any funding agency in the  
38  
39 367 public, commercial, or not-for-profit sectors.  
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42 368 **Competing Interests:** Kathleen Fairman is President and James Rucker is Research  
43  
44 369 Intern with Kathleen Fairman LTD, a for-profit research consulting firm. Kathleen  
45  
46 370 Fairman LTD provided analytic support and article processing charges but has no  
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48 371 financial or nonfinancial interests related to the topic of the manuscript. Kellie Goodlet  
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50 372 and Roy Zawadzki have no competing interests to report.  
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## 374 **Data Availability Statement**

375 All source data, analytic packages, and program code for all analyses in this report are  
376 publicly available using information and links provided at  
377 [https://github.com/JamesRucker/Unexplained\\_deaths](https://github.com/JamesRucker/Unexplained_deaths).

## 378 **Author Contributions**

379 KAF and KJG performed concept and design, assisted by JDR and RSZ. Analyses were  
380 performed by KAF and JDR, assisted by RSZ. The manuscript was drafted by KAF and  
381 revised for important content by all authors. All authors read and approved of the final  
382 manuscript. All authors agree to be accountable for all aspects of the work in ensuring  
383 that questions related to the accuracy or integrity of any part of the work are  
384 appropriately investigated and resolved.

## 385 **Patient and Public Involvement**

386 No patient involved. This study was a retrospective analysis of aggregated death  
387 certificate data.

## 388 **Ethics Statement**

389 No Institutional Review Board approval or exemption was sought, as this study was a  
390 retrospective analysis of publicly available, aggregated data with no identifying  
391 information.

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Table 1. Overview of Changes in Reported Deaths During Pandemic Periods, 2019-20 Versus Prior 5-Season Benchmark

	Total	Explained			Unexplained		
	All Causes	Reported UCOD, COVID-19	Reported UCOD, Not COVID-19 <sup>a</sup>	Total Explained <sup>b</sup>	UCOD Was NEC	Unreported: All-Cause Death, No UCOD <sup>c</sup>	Total Unexplained <sup>d</sup>
<b>Pandemic awareness period<sup>e</sup></b>							
Prior-season mean benchmark	546,260	0	383,245	383,245	6,106	156,909	163,015
2019-20	560,736	3,578	384,702	388,280	6,577	165,879	172,456
Change <sup>f</sup>	<b>14,476</b>	3,578	1,457	5,035	471	8,970	9,441
% of excess deaths	100.0%	24.7%	10.1%	34.8%	3.3%	62.0%	65.2%
<b>Initial pandemic peak period<sup>e</sup></b>							
Prior-season mean benchmark	453,618	0	315,900	315,900	5,175	132,543	137,718
2019-20	588,710	93,843	335,458	429,301	6,061	153,348	159,409
Change <sup>f</sup>	<b>135,092</b>	93,843	19,558	113,401	886	20,805	21,691
% of excess deaths	100.0%	69.5%	14.5%	83.9%	0.7%	15.4%	16.1%
<b>Pandemic post-peak<sup>e</sup></b>							
Prior-season mean benchmark	821,482	0	565,731	565,731	9,793	245,958	255,751
2019-20	978,181	82,482	594,026	676,508	15,345	286,328	301,673
Change <sup>f</sup>	<b>156,699</b>	82,482	28,295	110,777	5,552	40,370	45,922
% of excess deaths	100.0%	52.6%	18.1%	70.7%	3.5%	25.8%	29.3%
<b>Total changes, pandemic awareness through end of observation</b>							
Change <sup>f</sup>	<b>306,267</b>	179,903	49,311	229,214	6,909	70,145	77,054
% of excess deaths	100.0%	58.7%	16.1%	74.8%	2.3%	22.9%	25.2%

<sup>a</sup> Sum of specific causes other than COVID-19 reported in the mortality files, including heart disease, cancer, chronic lower respiratory disease, cerebrovascular disease, Alzheimer's disease, diabetes, influenza-pneumonia, other respiratory illness, kidney disease, and septicemia. Diagnosis codes for each category are in Supplement Appendix 1. <sup>b</sup> Sum of specific causes plus COVID-19. <sup>c</sup> All-cause deaths not reported in any of the categories of death included in the mortality files, including those listed in footnote a, NEC deaths, or COVID-19. <sup>d</sup> NEC deaths plus unreported deaths. <sup>e</sup> Pandemic awareness is from weeks 17-26 (January 19 through March 28 in 2019-20 season). Initial pandemic peak is from weeks 27-35 (March 29 through May 30 in 2019-20 season). Pandemic post-peak is from weeks 36-52 (May 31 through September 26 in 2019-20 season). <sup>f</sup> 2019-20 values minus benchmark values. Bolded numbers are excess deaths. COVID-19=coronavirus-19; NEC=not elsewhere classified; UCOD=underlying cause of death.

Figure 1 Legend

Figure 1. Trends in Population-Adjusted Death Counts by Week of Influenza Season,<sup>a</sup> 2014-15 Through 2019-20 Seasons

<sup>a</sup> For each influenza season, week 1 begins on approximately October 1 and week 52 ends on approximately September 30. A total of 312 weeks (52 weeks for 6 seasons) were included in the analyses. Dividing lines represent the ends of weeks 16 (week prior to pandemic awareness period), 26 (week prior to initial pandemic peak), and 35 (week prior to pandemic post-peak period). Prior-season benchmarks are means (deaths summed across seasons, divided by 2, 3, and 5, respectively, for 2-season, 3-season, and 5-season benchmarks). <sup>b</sup> Explained deaths include specific causes reported in the mortality files, including heart disease, cancer, chronic lower respiratory disease, cerebrovascular disease, Alzheimer's disease, diabetes, influenza-pneumonia, other respiratory illness, kidney disease, septicemia, and COVID-19. Diagnosis codes for each category are in Supplement Appendix 1. Unexplained deaths are all-cause deaths with no reported underlying cause or with a not elsewhere classified (NEC) cause (all-cause deaths minus explained deaths). NEC deaths are described in ICD-10 nomenclature as "symptoms, signs, and abnormal clinical and laboratory findings not elsewhere classified" (ICD-10 range R00-R99), include "ill-defined and unknown cause of mortality" (R99), a code commonly used pending forensic investigation of injurious death.<sup>23,24</sup> COVID-19=coronavirus-19; ICD=International Classification of Diseases; NEC=not elsewhere classified.

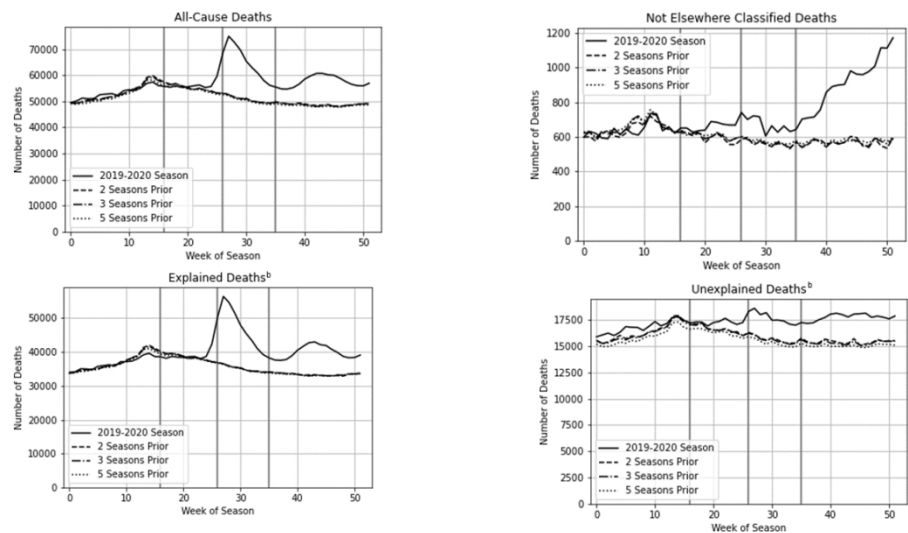


Figure 1. Trends in Population-Adjusted Death Counts by Week of Influenza Season,a 2014-15 Through 2019-20 Seasons

a For each influenza season, week 1 begins on approximately October 1 and week 52 ends on approximately September 30. A total of 312 weeks (52 weeks for 6 seasons) were included in the analyses. Dividing lines represent the ends of weeks 16 (week prior to pandemic awareness period), 26 (week prior to initial pandemic peak), and 35 (week prior to pandemic post-peak period). Prior-season benchmarks are means (deaths summed across seasons, divided by 2, 3, and 5, respectively, for 2-season, 3-season, and 5-season benchmarks). b Explained deaths include specific causes reported in the mortality files, including heart disease, cancer, chronic lower respiratory disease, cerebrovascular disease, Alzheimer’s disease, diabetes, influenza-pneumonia, other respiratory illness, kidney disease, septicemia, and COVID-19. Diagnosis codes for each category are in Supplement Appendix 1. Unexplained deaths are all-cause deaths with no reported underlying cause or with a not elsewhere classified (NEC) cause (all-cause deaths minus explained deaths). NEC deaths are described in ICD-10 nomenclature as “symptoms, signs, and abnormal clinical and laboratory findings not elsewhere classified” (ICD-10 range R00-R99), include “ill-defined and unknown cause of mortality” (R99), a code commonly used pending forensic investigation of injurious death.<sup>23,24</sup> COVID-19=coronavirus-19; ICD=International Classification of Diseases; NEC=not elsewhere classified.

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1 Appendix 1. ICD-10 Category Descriptions in NCHS Files, Ranked in Descending Order  
 2 by U.S. Death Counts in 2017<sup>8</sup>

<b>NCHS Category: Diseases of the Heart (I00-I09; I11 I13; I20-I51)</b>	
I00-I02 Acute rheumatic fever	
I05-I09 Chronic rheumatic heart diseases;	
I11 Hypertensive heart disease	
I13 Hypertensive heart and chronic kidney disease	
I20 Angina pectoris	
I21 Acute myocardial infarction	
I22 Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction	
I23 Certain complications following ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction (within the 28 day period)	
I24 Other acute ischemic heart diseases	
I25 Chronic ischemic heart disease	
I26-I28 Pulmonary heart disease and diseases of pulmonary circulation	
I30 Acute pericarditis	
I31 Other diseases of pericardium	
I32 Pericarditis in diseases classified elsewhere	
I33 Acute and subacute endocarditis	
I34 Nonrheumatic mitral valve disorders	
I35 Nonrheumatic aortic valve disorders	
I36 Nonrheumatic tricuspid valve disorders	
I37 Nonrheumatic pulmonary valve disorders	
I38 Endocarditis, valve unspecified	
I39 Endocarditis and heart valve disorders in diseases classified elsewhere	
I40 Acute myocarditis	
I41 Myocarditis in diseases classified elsewhere	
I42 Cardiomyopathy	
I43 Cardiomyopathy in diseases classified elsewhere	
I44 Atrioventricular and left bundle-branch block	
I45 Other conduction disorders	
I46 Cardiac arrest	
I47 Paroxysmal tachycardia	
I48 Atrial fibrillation and flutter	
I49 Other cardiac arrhythmias	
I50 Heart failure	
I51 Complications and ill-defined descriptions of heart disease	
<b>NCHS Category: Malignant Neoplasms (C00-C97)</b>	
Code range includes malignant neoplasms of all types	
<b>NCHS Category: Chronic Lower Respiratory Disease (J40-J47)</b>	
J40 Bronchitis, not specified as acute or chronic	
J41 Simple and mucopurulent chronic bronchitis	
J42 Unspecified chronic bronchitis	
J43 Emphysema	
J44 Other chronic obstructive pulmonary disease	
J45 Asthma	
J46 Status asthmaticus	
J47 Bronchiectasis	
<b>NCHS Category: Cerebrovascular Disease (I60-I69)</b>	
I60 Nontraumatic subarachnoid hemorrhage	
I61 Nontraumatic intracerebral hemorrhage	
I62 Other and unspecified nontraumatic intracranial hemorrhage	
I63 Cerebral infarction	
I64 Stroke, not specified if hemorrhagic or infarct	

I65	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction
I66	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction
I67	Other cerebrovascular diseases
I68	Cerebrovascular disorders in diseases classified elsewhere
I69	Sequelae of cerebrovascular disease
<b>NCHS Category: Alzheimer's Disease (G30)</b>	
G30	Alzheimer's disease
<b>NCHS Category: Diabetes (E10-E14)</b>	
E10	Type 1 diabetes mellitus
E11	Type 2 diabetes mellitus
E13	Other specified diabetes mellitus
E14	is an old code for unspecified diabetes mellitus
<b>NCHS Category: Influenza and Pneumonia (J10-J18)</b>	
J10	Influenza due to other identified influenza virus
J11	Influenza due to unidentified influenza virus
J12	Viral pneumonia, not elsewhere classified
J13	Pneumonia due to Streptococcus pneumoniae
J14	Pneumonia due to Hemophilus influenzae
J15	Bacterial pneumonia, not elsewhere classified
J16	Pneumonia due to other infectious organisms, not elsewhere classified
J17	Pneumonia in diseases classified elsewhere
J18	Pneumonia, unspecified organism
<b>NCHS Category: Nephritis, Nephrotic Syndrome, and Nephrosis (N00-N07, N17-N19, N25-N27)</b>	
N00	Acute nephritic syndrome
N01	Rapidly progressive nephritic syndrome
N02	Recurrent and persistent hematuria
N03	Chronic nephritic syndrome
N04	Nephrotic syndrome
N05	Unspecified nephritic syndrome
N06	Isolated proteinuria with specified morphological lesion
N07	Hereditary nephropathy, not elsewhere classified
N17	Acute kidney failure
N18	Chronic kidney disease
N19	Unspecified kidney failure
N25	Disorders resulting from impaired renal tubular function
N26	Unspecified contracted kidney
N27	Small kidney of unknown cause
<b>NCHS Category: Other Diseases of the Respiratory System (J00-J06,J30-J39,J67,J70-J98)</b>	
J00	Acute nasopharyngitis [common cold]
J01	Acute sinusitis
J02	Acute pharyngitis
J03	Acute tonsillitis
J04	Acute laryngitis and tracheitis
J05	Acute obstructive laryngitis [croup] and epiglottitis
J06	Acute upper respiratory infections of multiple and unspecified sites
J30	Vasomotor and allergic rhinitis
J31	Chronic rhinitis, nasopharyngitis and pharyngitis
J32	Chronic sinusitis
J33	Nasal polyp
J34	Other and unspecified disorders of nose and nasal sinuses
J35	Chronic diseases of tonsils and adenoids
J36	Peritonsillar abscess
J37	Chronic laryngitis and laryngotracheitis
J38	Diseases of vocal cords and larynx, not elsewhere classified
J39	Other diseases of upper respiratory tract

J67	Hypersensitivity pneumonitis due to organic dust
J70	Respiratory conditions due to other external agents
J80	Acute respiratory distress syndrome
J81	Pulmonary edema
J82	Pulmonary eosinophilia, not elsewhere classified
J84	Other interstitial pulmonary diseases
J85	Abscess of lung and mediastinum
J86	Pyothorax
J90	Pleural effusion, not elsewhere classified
J91	Pleural effusion in conditions classified elsewhere
J92	Pleural plaque
J93	Pneumothorax and air leak
J94	Other pleural conditions
J95-J95	Intraoperative and postprocedural complications and disorders of respiratory system, not elsewhere classified
J96	Respiratory failure, not elsewhere classified
J98	Other respiratory disorders
<b>NCHS Category: Septicemia (A40-A41)</b>	
A40	Streptococcal sepsis
A41	Other sepsis
<b>NCHS Category: Symptoms, Signs, and Abnormal Clinical and Laboratory Findings (R00-R99)</b>	
R00-R09	Symptoms and signs involving the circulatory and respiratory systems
R10-R19	Symptoms and signs involving the digestive system and abdomen
R20-R23	Symptoms and signs involving the skin and subcutaneous tissue
R25-R29	Symptoms and signs involving the nervous and musculoskeletal systems
R30-R39	Symptoms and signs involving the genitourinary system
R40-R46	Symptoms and signs involving cognition, perception, emotional state and behavior
R47-R49	Symptoms and signs involving speech and voice
R50-R69	General symptoms and signs
R70-R79	Abnormal findings on examination of blood, without diagnosis
R80-R82	Abnormal findings on examination of urine, without diagnosis
R83-R89	Abnormal findings on examination of other body fluids, substances and tissues, without diagnosis
R90-R94	Abnormal findings on diagnostic imaging and in function studies, without diagnosis
R97-R97	Abnormal tumor markers
R99-R99	Ill-defined and unknown cause of mortality
<b>NCHS Category: COVID-19</b>	
U071	COVID-19

COVID-19=coronavirus-19; ICD=International Classification of Diseases codes available at <https://www.icd10data.com/>;  
NCHS=National Center for Health Statistics

6 Appendix 2. Overview of Changes in Reported Deaths During Pandemic Periods, 2019-20 Versus Prior 2-Season and 3-  
7 Season Benchmarks

	Total	Explained			Unexplained		
	All Causes	Reported UCOD, COVID-19	Reported UCOD, Not COVID-19 <sup>a</sup>	Total Explained <sup>b</sup>	UCOD Was NEC	Unreported: All-Cause Death, No UCOD <sup>c</sup>	Total Unexplained <sup>d</sup>
<b>Pandemic awareness period<sup>e</sup></b>							
Prior-season mean, 2-season benchmark	551,845	0	385,438	385,438	5,971	160,437	166,408
Prior-season mean, 3-season benchmark	551,951	0	385,863	385,863	6,058	160,030	166,088
2019-20	560,736	3,578	384,702	388,280	6,577	165,879	172,456
Change, 2-season benchmark <sup>f</sup>	<b>8,891</b>	3,578	-736	2,842	606	5,442	6,048
Change, 3-season benchmark <sup>f</sup>	<b>8,785</b>	3,578	-1,161	2,417	519	5,849	6,368
% of excess deaths, 2-season benchmark	100.0%	40.2%	-8.3%	32.0%	6.8%	61.2%	68.0%
% of excess deaths, 3-season benchmark	100.0%	40.7%	-13.2%	27.5%	5.9%	66.6%	72.5%
<b>Initial pandemic peak period<sup>e</sup></b>							
Prior-season mean, 2-season benchmark	458,044	0	317,107	317,107	5,051	135,886	140,937
Prior-season mean, 3-season benchmark	457,300	0	316,944	316,944	5,096	135,260	140,356
2019-20	588,710	93,843	335,458	429,301	6,061	153,348	159,409
Change, 2-season benchmark <sup>f</sup>	<b>130,666</b>	93,843	18,351	112,194	1,010	17,462	18,472
Change, 3-season benchmark <sup>f</sup>	<b>131,410</b>	93,843	18,514	112,357	965	18,088	19,053
% of excess deaths, 2-season benchmark	100.0%	71.8%	14.0%	85.9%	0.8%	13.4%	14.1%
% of excess deaths, 3-season benchmark	100.0%	71.4%	14.1%	85.5%	0.7%	13.8%	14.5%
<b>Pandemic post-peak<sup>e</sup></b>							
Prior-season mean, 2-season benchmark	829,780	0	567,619	567,619	9,639	252,522	262,161
Prior-season mean, 3-season benchmark	827,727	0	567,244	567,244	9,634	250,850	260,484
2019-20	978,181	82,482	594,026	676,508	15,345	286,328	301,673
Change, 2-season benchmark <sup>f</sup>	<b>148,401</b>	82,482	26,407	108,889	5,706	33,806	39,512
Change, 3-season benchmark <sup>f</sup>	<b>150,454</b>	82,482	26,782	109,264	5,711	35,478	41,189
% of excess deaths, 2-season benchmark	100.0%	55.6%	17.8%	73.4%	3.8%	22.8%	26.6%
% of excess deaths, 3-season benchmark	100.0%	54.8%	17.8%	72.6%	3.8%	23.6%	27.4%
<b>Total changes, pandemic awareness through end of observation</b>							
2-season benchmark <sup>f</sup>	<b>287,957</b>	179,903	44,022	223,925	7,322	56,709	64,032
% of excess deaths, 2-season benchmark	100.0%	62.5%	15.3%	77.8%	2.5%	19.7%	22.2%
3-season benchmark <sup>f</sup>	<b>290,649</b>	179,903	44,136	224,039	7,195	59,415	66,610
% of excess deaths, 3-season benchmark	100.0%	61.9%	15.2%	77.1%	2.5%	20.4%	22.9%

<sup>a</sup> Sum of specific causes other than COVID-19 reported in the mortality files, including heart disease, cancer, chronic lower respiratory disease, cerebrovascular disease, Alzheimer's disease, diabetes, influenza-pneumonia, other respiratory illness, kidney disease, and septicemia. Diagnosis codes for each category are in Appendix 1. <sup>b</sup> Sum of specific causes plus COVID-19. <sup>c</sup> All-cause deaths not reported in any of the categories of death included in the mortality files, including those listed in footnote a, NEC deaths, or COVID-19. <sup>d</sup> NEC deaths plus unreported deaths. <sup>e</sup> Pandemic awareness is from weeks 17-26 (January 19 through March 28 in 2019-20 season). Initial pandemic peak is from weeks 27-35 (March 29 through May 30 in 2019-20 season). Pandemic post-peak is from weeks 36-52 (May 31 through September 26 in 2019-20 season). <sup>f</sup> 2019-20 values minus benchmark values. Bolded numbers are excess deaths. COVID-19=coronavirus-19; NEC=not elsewhere classified; UCOD=underlying cause of death.

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
<b>Title and abstract</b>					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	Retrospective analysis--title, page 1  Abstract, page 3	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included.  RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract.  RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Type of data: death certificates--title, page 1  Name of database--abstract, page 2  Region--U.S., title, page 1  Timeframe--abstract, page 2
<b>Introduction</b>					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Pages 5-6		
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 6, last paragraph of introduction		
<b>Methods</b>					
Study Design	4	Present key elements of study design early in the paper	Title, page 1 Abstract, page 2 First paragraph of methods, page 7		
Setting	5	Describe the setting, locations, and relevant dates, including	Page 7		

		periods of recruitment, exposure, follow-up, and data collection			
Participants	6	<p>(a) <i>Cohort study</i> - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up</p> <p><i>Case-control study</i> - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls</p> <p><i>Cross-sectional study</i> - Give the eligibility criteria, and the sources and methods of selection of participants</p> <p>(b) <i>Cohort study</i> - For matched studies, give matching criteria and number of exposed and unexposed</p> <p><i>Case-control study</i> - For matched studies, give matching criteria and the number of controls per case</p>	Page 7	<p>RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided.</p> <p>RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided.</p> <p>RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.</p>	<p>Appendix 1</p> <p>Inapplicable, but previous uses of database are described on page 5</p> <p>Inapplicable—no linkage</p>
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	<p>Outcome—page 7</p> <p>Diagnosis codes—Appendix 1</p>	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Appendix 1
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement).	Pages 7-8		

		Describe comparability of assessment methods if there is more than one group	Inapplicable—one population group		
Bias	9	Describe any efforts to address potential sources of bias	Inapplicable—descriptive analysis of single population		
Study size	10	Explain how the study size was arrived at	Inapplicable—population		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Page 7		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) <i>Cohort study</i> - If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> - If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	Page 7  Inapplicable  Inapplicable  Inapplicable		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database	Page 7 – data are publicly available online

				population used to create the study population.	
				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	Inapplicable
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Inapplicable—no linkages
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study ( <i>e.g.</i> , numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		RECORD 13.1: Describe in detail the selection of the persons included in the study ( <i>i.e.</i> , study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Inapplicable—100% of deaths in 48 states, page 6
Descriptive data	14	(a) Give characteristics of study participants ( <i>e.g.</i> , demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) <i>Cohort study</i> - summarise follow-up time ( <i>e.g.</i> , average and total amount)	First paragraph of Results, page 8  Inapplicable—unreported (missing) cause of death is the topic of the study		

Outcome data	15	<p><i>Cohort study</i> - Report numbers of outcome events or summary measures over time</p> <p><i>Case-control study</i> - Report numbers in each exposure category, or summary measures of exposure</p> <p><i>Cross-sectional study</i> - Report numbers of outcome events or summary measures</p>	Page 7		
Main results	16	<p>(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included</p> <p>(b) Report category boundaries when continuous variables were categorized</p> <p>(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period</p>	<p>All estimates are unadjusted; population data, CIs inapplicable</p> <p>Inapplicable</p>		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Inapplicable		
<b>Discussion</b>					
Key results	18	Summarise key results with reference to study objectives	Page 9, first paragraph of Discussion		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 9, first paragraph of Discussion	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing	Classification and changes over time were topics of the study

				data, and changing eligibility over time, as they pertain to the study being reported.	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Pages 9-10		
Generalisability	21	Discuss the generalisability (external validity) of the study results	Inapplicable—population data		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	No external funding but work was supported by authors' employers—page 11		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Reference #8, page 14, link to Github site with all data and code

\*Reference: Benchimol EI, Smeeth L, Guttman A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

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# BMJ Open

## Unexplained Mortality During the U.S. COVID-19 Pandemic: Retrospective Analysis of Death Certificate Data and Critical Assessment of Excess Death Calculations

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-050361.R2
Article Type:	Original research
Date Submitted by the Author:	30-Sep-2021
Complete List of Authors:	Fairman, Kathleen; Midwestern University College of Pharmacy - Glendale, Department of Pharmacy Practice; Kathleen Fairman LTD Goodlet, Kellie; Midwestern University College of Pharmacy - Glendale, Department of Pharmacy Practice Rucker, James; Kathleen Fairman LTD Zawadzki, Roy; University of California Irvine
<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Public health, Mental health, Health policy, Health informatics
Keywords:	COVID-19, EPIDEMIOLOGY, MENTAL HEALTH, PUBLIC HEALTH, STATISTICS & RESEARCH METHODS, Health informatics < BIOTECHNOLOGY & BIOINFORMATICS

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Retrospective Analysis of Death Certificate Data and Critical Assessment of  
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Word count: 2851    Tables: 1    Figures: 1    Appendix: 3

Keywords: COVID-19, mortality, death certification, epidemiological methods, mental health

Abstract

Objectives: Cause-of-death discrepancies are common in respiratory illness-related mortality. A standard epidemiological metric, excess all-cause death, is unaffected by these discrepancies but provides no actionable policy information when increased all-cause mortality is unexplained by reported specific causes. To assess the contribution of unexplained mortality to the excess-death metric, we parsed excess deaths in the coronavirus-2019 (COVID-19) pandemic into changes in explained versus unexplained (unreported or unspecified) causes.

Design: Retrospective repeated cross-sectional analysis, U.S. death-certificate data for 6 influenza seasons beginning October 2014, comparing population-adjusted historical benchmarks from the previous 2, 3, and 5 seasons with 2019-20.

Setting: 48 of 50 states with complete data.

Participants: 16.3 million deaths in 312 weeks, reported in categories—all causes, top 8 natural causes, and respiratory causes including COVID-19.

Outcome Measures: Change in population-adjusted counts of deaths from seasonal benchmarks to 2019-20, from all causes (i.e., total excess deaths) and from explained versus unexplained causes, reported for the season overall and for time periods defined *a priori*: pandemic awareness (January 19 through March 28); initial pandemic peak (March 29 through May 30); and pandemic post-peak (May 31 through September 26).

Results: Depending on seasonal benchmark, 287,957-306,267 excess deaths occurred through September 2020: 179,903 (58.7%-62.5%) attributed to COVID-19; 44,022-49,311 (15.2%-16.1%) to other reported causes; 64,032-77,054 (22.2%-25.2%) unexplained (unspecified or unreported cause). Unexplained deaths constituted 65.2%-

72.5% of excess deaths from January 19 to March 28 and 14.1%-16.1% from March 29 through May 30.

Conclusions: Unexplained mortality contributed substantially to U.S. pandemic-period excess deaths. Onset of unexplained mortality in February 2020 coincided with previously reported increases in psychotropic use, suggesting possible psychiatric or injurious causes. Because underlying causes of unexplained deaths may vary by group or region, results suggest excess death calculations provide limited actionable information, supporting previous calls for improved cause-of-death data to support evidence-based policy.

**Strengths and limitations of this study**

This is the first study to assess the degree to which mortality from unreported or unspecified causes contributed to excess deaths in the U.S. coronavirus-19 (COVID-19) pandemic, raising important policy questions about the utility of the excess-death metric.

We used population-adjusted U.S. national data, accounting for deaths in every category reported by the National Center for Health Statistics (NCHS), including top natural causes and respiratory causes including COVID-19.

Our statistical analysis was descriptive, but our estimates of excess deaths are similar to those previously developed using more sophisticated statistical analyses of the same data files.

Study results generalize to the United States through September 26, 2020, but not to other countries, as cause-of-death attribution practices vary cross-nationally, or to other pandemic periods, including the COVID-19 case surge in late 2020.

Although we cite evidence suggesting many of the unspecified-cause deaths may have been due to suicide, overdose, or underlying psychiatric causes, we were unable to address this question using the available NCHS data files, particularly in population subgroups that may have been especially vulnerable to injurious causes of mortality during the pandemic.

## Introduction

Errors in cause-of-death attribution (CODA) are common in infectious respiratory illness, compromising accurate tracking of disease impact and spread.<sup>1-3</sup> CODA is especially challenging in coronavirus disease 2019 (COVID-19) because of competing causes of mortality, including cancer, lung disease, obesity-related conditions, and superannuation.<sup>4</sup> Compounding this problem, key factors contributing to COVID-19 CODA, such as level of training and expertise of mortality coders, whether laboratory testing is or is not required, financial incentives for reporting, and public health delivery systems, vary considerably by country.<sup>5,6</sup> These variations make cross-national comparisons of COVID-19-attributed mortality problematic, threatening the accuracy of the virus mortality statistics needed for public health decision making.<sup>3</sup>

A standard metric generally understood to account for these discrepancies is “excess death,” defined as mortality from all causes exceeding that expected from historical experience.<sup>7</sup> Recent investigators have calculated excess deaths to estimate U.S. COVID-19 impact, using death certificate data made available by the U.S. National Center for Health Statistics (NCHS).<sup>7-9</sup> Most interpretations of excess death calculations reflect an underlying assumption that 100% of the change in mortality that took place during the pandemic was attributable, indirectly or directly, to COVID-19.<sup>7,8,10</sup> The calculation has the advantages of no reliance on CODA, because it considers only all-cause deaths, and of accounting for deaths due to undetected COVID-19 or to use of scarce health system resources by infected patients.<sup>7,8,10</sup>

Despite these advantages, the utility and interpretation of excess death calculations may be compromised by unexplained deaths. Fully adjudicated, final U.S.

mortality files report specific causes or contributing factors, as well as demographic characteristics, for each individual decedent.<sup>11,12</sup> In contrast, files made available by the NCHS beginning in May 2020 to facilitate pandemic-mortality analysis, which have been used to calculate excess deaths as an indication of the “full COVID-19 burden,”<sup>8</sup> report only aggregated (summed) weekly death counts, grouped into broad diagnostic categories.<sup>13,14</sup> These categories, shown in Supplement Appendix 1, represent ranges of International Classification of Diseases, Tenth Revision (ICD-10) diagnosis codes.<sup>13,14</sup> For excess deaths unexplained by these causes, the true underlying causes are unknown, despite presumably representing appropriate policy targets. For example, markedly different interventions would be suggested by unexplained deaths due to undetected COVID-19, high-speed automobile accidents on empty highways,<sup>15</sup> or delayed care for life-threatening conditions when people fear using available emergency department capacity.<sup>16</sup>

Risk factors for potential causes of unexplained death vary cross-nationally. For example, U.S. opioid supplies, opioid mortality, substance use disorder prevalence, and suicide rates far exceed those of other high-income nations,<sup>17</sup> suggesting greater psychological vulnerability to pandemic-period disruptions. Yet, neither substance misuse nor mental illness is recorded as a cause of death in the currently available NCHS pandemic period mortality files.<sup>13,14</sup> Risk factors for COVID-19 mortality, such as obesity, smoking, and healthcare associated infections, also demonstrate considerable cross-national variability.<sup>17</sup>

Quantifying unexplained excess deaths would provide information about the degree to which the utility and interpretation of excess death calculations are potentially

compromised by unreported or unspecified causes of mortality. Moreover, assessing the timing of unexplained deaths at various pandemic phases would inform current discussions about societal factors that may contribute to pandemic-period morbidity and mortality, such as fear of contagion or economic vulnerability.<sup>18-20</sup> Accordingly, we used publicly available NCHS mortality data files for the past 6 influenza seasons to calculate the timing and extent of changes in all-cause deaths that were explained versus unexplained by changes in reported causes.

The primary research question was to what degree unexplained mortality contributed to excess mortality during the pandemic. Because the excess mortality calculation represents change in mortality compared with historical experience, we addressed this research question by assessing the contributions of changes in explained versus unexplained causes of death to change in total, all-cause death. A secondary research question, intended to provide exploratory information about possible reasons for unexplained mortality, was when unexplained deaths escalated in 2020. We formulated both research questions, *a priori* to this project, after noticing large numbers of unexplained deaths in analyses for a different exploratory study on cause-of-death attribution.<sup>21</sup>

## Methods

### *Design and Data Source*

This study was a retrospective, repeated cross-sectional analysis of U.S. mortality files made available by the NCHS beginning in 2020 for pandemic-period analysis. The data files for 2020 represent provisional causes of death.<sup>13</sup> The corresponding data files for 2014-2019 represent final adjudicated causes of death,<sup>14</sup>

reported in the same broad diagnostic categories as the 2020 data to facilitate analysis (Supplement Appendix 1).

The study measures were based on reported underlying cause of death (UCOD), defined as “the disease or injury which initiated the train of morbid events leading directly to death.”<sup>22</sup> Only one UCOD is reported on each death certificate. The study files include weekly counts of deaths in total (all-cause) and by UCOD category, grouped by state.

In addition to categories representing the top 8 U.S. causes of natural death (heart disease, cancer, chronic lower respiratory disease, cerebrovascular disease, Alzheimer’s disease, diabetes, influenza and pneumonia, and kidney disease), which together accounted for 66% of all U.S. deaths in 2017,<sup>23</sup> the files include four additional categories: miscellaneous respiratory conditions, (e.g., nasopharyngitis, sinusitis, pneumothorax); septicemia; COVID-19; and nonspecific-cause deaths.<sup>13,14</sup> Nonspecific-cause deaths, described in ICD-10 nomenclature as “symptoms, signs, and abnormal clinical and laboratory findings not elsewhere classified” (NEC; ICD-10 range R00-R99), include “ill-defined and unknown cause of mortality” (R99),<sup>13,14</sup> a code commonly used pending forensic investigation of injurious death.<sup>24</sup> Neither the 2020 provisional data nor the corresponding grouped data for 2014-2019 include reporting categories for specific psychiatric causes, including substance use disorders (ICD-10 codes F00-F99 excluding developmental disorders), or for injurious deaths including intentional self-harm (ICD-10 codes X71-X83) and unintentional overdose (ICD-10 codes T36-T50, excluding codes for underdosing).<sup>25</sup>

*Data Analyses*

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3 Data from October 5, 2014, through September 26, 2020, were downloaded on  
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5 January 22, 2021. Analyses were performed using open-source analytic tools.<sup>11</sup>  
6  
7 Specifically, Python coding was used with Pandas, a data-organization tool,<sup>26,27</sup> to  
8  
9 group data into 6 influenza seasons, 52 weeks each. Using the same software tools,  
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11 data for the 2014-15 to 2018-19 seasons were population-adjusted to July 2019 using  
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13 U.S. Census data.<sup>11,28</sup> As in previous research, Connecticut and North Carolina were  
14  
15 excluded because of incomplete reporting.<sup>8</sup> Data were further grouped *a priori* into time  
16  
17 periods roughly corresponding to U.S. trends in COVID-19 mortality: pandemic  
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19 awareness (January 19 through March 28); initial pandemic peak (March 29 through  
20  
21 awareness (January 19 through March 28); initial pandemic peak (March 29 through  
22  
23 May 30); and pandemic post-peak (May 31 through September 26).<sup>11,29</sup>  
24  
25

26 Analyses were descriptive to facilitate the parsing of excess death (i.e., change in  
27  
28 all-cause death) into explained and unexplained proportions. The decision was in  
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30 accordance with the principle of parsimony in data presentation,<sup>30</sup> as we found that  
31  
32 descriptive results were similar to those produced using more sophisticated  
33  
34 techniques.<sup>8,9</sup> For each week, time period, and diagnostic category, we calculated prior-  
35  
36 season averages for 3 historical benchmark periods: 2 seasons (2017-18 to 2018-19), 3  
37  
38 seasons (2016-17 to 2018-19), and 5 seasons (2014-15 to 2018-19). Averages were  
39  
40 calculated as total death count for the indicated time period, divided by number of years.  
41  
42 For example, the 2-season average for week 1 was the sum of week 1 deaths reported  
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44 in 2017-18 and 2018-19, divided by 2. Three benchmark time periods were used  
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46 because it is common to compare current-year mortality data with several historical  
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48 benchmarks,<sup>31</sup> consistent with the need to report sensitivity analyses of epidemiological  
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data.<sup>32</sup> Weekly prior-season averages and 2019-20 counts were graphed using Matplotlib.<sup>33</sup>

For each week and time period, excess deaths were defined *a priori* as increases in all-cause deaths over the population-adjusted prior-season mean benchmarks (i.e., 2019-20 season values minus benchmark values). Unexplained deaths were defined as all-cause deaths either not reported in any diagnostic category (unreported) or reported in the NEC category (unspecified). Explained deaths were defined as all-cause deaths reported in any of the specific cause-of-death categories (i.e., all-cause minus unexplained deaths). Changes in explained and unexplained causes were calculated using the same method as for excess deaths, by first calculating the population-adjusted prior-season mean benchmarks, then subtracting the benchmark values from the 2019-20 season values.

Results

Of a total of 16.3 million all-cause deaths reported over 6 influenza seasons in 48 states, 2.98 million occurred during 2019-20, representing a population-adjusted increase of 288,467-319,858 excess deaths over prior-season averages for 2, 3, and 5 years (Figure 1, top). Mean annual population-adjusted total all-cause death counts varied modestly across seasonal benchmarks, ranging from 2,659,228 to 2,690,619. An increase in NEC deaths began in approximately week 19 and escalated sharply beginning at week 36 (May 31 in the 2019-20 season) through end of observation. Increases in explained and unexplained deaths, respectively, began in approximately week 25 (March 15-March in 2020) and week 20 (February 9-February 15 in 2020; Figure 1, bottom).

Contribution of unexplained mortality to excess deaths varied considerably by pandemic period (Table 1; Supplement Appendix 2). Using the 5-year benchmark, of the total increase of 306,267 all-cause deaths reported from pandemic awareness through end of observation (seasonal weeks 17-52, January 19 through September 26, 2020), 179,903 (58.7%) were attributed to COVID-19; 49,311 (16.1%) to changes in reported causes other than COVID-19; 6,909 (2.3%) to increased NEC deaths; and 70,145 (22.9%) to increases in deaths with no reported cause. On a proportional basis, mortality change with unexplained (unreported or NEC) cause was much greater in the pandemic awareness period (January 19 through March 28, 65.2% of change in all-cause deaths) than in the initial pandemic peak period (March 29 through May 30, 16.1%) or the post-peak period (May 31 through September 26, 29.3%). In total, an increase of 77,054 unexplained deaths was responsible for 25.2% of change in all-cause mortality from January 19 through September 26, 2020.

Results using the 2- and 3-year benchmarks were similar (Supplement Appendix 3). Using these benchmarks, increases in unexplained deaths accounted for 68.0%-72.5% of excess deaths during the pandemic awareness period; 14.1%-14.5% of excess deaths during initial peak; and 26.6%-27.4% of excess deaths in the pandemic post-peak period. Measured from pandemic awareness through the end of observation, changes in unexplained deaths accounted for 22.2%-22.9% of excess deaths.

## Discussion

This analysis of population-adjusted U.S. death certificate data for 6 influenza seasons, the first to assess the extent and timing of unexplained pandemic deaths, indicated substantial impact of unexplained deaths on excess pandemic-period mortality. The most important study limitation is that observation ended on September

26, 2020. Results may not apply to subsequent disease activity, including the surge late in 2020,<sup>29</sup> or to other countries. Additionally, this analysis was descriptive, although it produced results for all-cause deaths similar to those using more sophisticated statistical methods.<sup>8,9</sup> For example, the 299,028 excess deaths estimated by the CDC using Poisson regression modeling through October 3, 2020<sup>9</sup> is comparable to our estimate of 287,957-306,267 excess deaths through September 26, 2020.

Despite these limitations, the finding that a large proportion of 2020 excess mortality was unexplained by changes in top causes of natural death or respiratory disease suggests a need to extend thinking about pandemic mortality beyond COVID-19 or its physical sequelae. Although drug overdoses and suicides are not reported in the available NCHS data, several factors implicate these as potential causes of the unexplained U.S. deaths. These include reports of increases in rates of serious psychological distress from 3.9% of adults in 2018 to 13.6% in April 2020<sup>20</sup> and of an 18.2% increase in 12-month overdose death rates from June 2019 to May 2020.<sup>34</sup> The increase in NEC deaths, which accelerated sharply beginning in approximately May 2020, is also consistent with this explanation because the R99 category included in the ICD-10 NEC group is commonly used pending forensic investigation of injurious death, introducing a lag period before cause-of-death determination.<sup>24</sup> However, the NEC increases could also represent COVID-19 not yet diagnosed because of pending laboratory testing.

Countering suicides but supporting overdose as causal factors underlying the unexplained deaths, recently released U.S. mortality data reported through August 2020 suggested early pandemic-period increases in overdoses, homicides, and unintentional

injuries, but decreases in suicides and motor vehicle accidents, relative to historical experience.<sup>35</sup> An important caveat to these early findings is that they represent the U.S. as a whole, possibly masking outcomes in economically and socially vulnerable populations that were already at increased risk of behavioral health-related mortality prior to the pandemic.<sup>36-39</sup> Among these are young adults, described in a U.S. Substance Abuse and Mental Health Services (SAMHSA) report as “a uniquely vulnerable population” based on pandemic-period data on anxiety, depression, traumatic stress, psychological distress, loneliness, substance misuse, and suicidal ideation.<sup>37</sup> Also at elevated risk were women, racial and ethnic minorities, health care workers, and pediatric populations.<sup>36-39</sup> These disparate behavioral health effects suggest that the underlying causes of excess deaths should be explored in U.S. population subgroups, rather than only for the nation as a whole.

Also supporting the interpretation of possible behavioral health effects, the timing of onset of unexplained deaths in February 2020 suggests they did not result from COVID-19 or sequelae of COVID-19 deaths (e.g., bereavement). Increases in unexplained deaths began about 4-6 weeks before >1,000 COVID-19 cases had been reported nationwide,<sup>29</sup> approximately coinciding with extensive media coverage of COVID-19<sup>40</sup> and a nationwide increase in use of psychotropic medications for anxiety, depression, and sleep disorders.<sup>41</sup> Also supporting this interpretation are survey data from early in the pandemic, suggesting no significant association between psychological distress and personal acquaintance with someone who died of COVID-19<sup>42</sup> but strong associations with fear of COVID-19 contagion and of disruption to finances and employment.<sup>18,20</sup>

Moreover, a content analysis of media coverage of the pandemic, posted as a nonpeer-reviewed working paper in November 2020, found that 91% of U.S. major media stories, compared with 54% of non-U.S. stories and 65% of scientific journal reports, were “negative in tone.”<sup>43</sup> These preliminary findings suggest a possible bias unique to U.S. media coverage of COVID-19. If confirmed with peer-reviewed research, the connection between this bias and psychological distress should be explored in additional studies. Neither the psychological effects of media coverage nor the specific causes of the unexplained deaths we observed could be assessed with available provisional mortality data. However, release of the full, final U.S. cause-of-death file for 2020, which likely will occur by early 2022, will make analyses of psychiatric and injurious causes of death, overall and by demographic and regional subgroups, feasible.

Expanding pandemic-period mortality research to include societal causes would help to evaluate a concern expressed by the Substance Abuse and Mental Health Services Administration about public health harms caused by focus “solely [on] virus containment” rather than on “all aspects of health.”<sup>44</sup> The addition of new UCOD categories for behavioral disorders, including psychiatric and substance use disorders, intentional self-harm, and unintentional overdose, to the available files would facilitate this investigation. Together, these causes accounted for approximately 106,000 U.S. deaths per year from 2010-2018,<sup>45</sup> and their prevalence as UCODs has increased rapidly over time.<sup>46-47</sup> The provisional files released by the NCHS in March of 2021, which included the diagnostic categories assessed in this research plus categories for accidents, intentional self-harm, homicide, and drug overdoses,<sup>48</sup> were aggregated monthly for the U.S. as a whole and therefore do not facilitate comparative policy

analysis, such as by states with varying pandemic policies (e.g., strict stay-at-home orders versus precautionary warnings).

Findings also suggest challenges in interpreting excess death reports because of between-group differences in predispositions to various causes of death.<sup>17,42</sup> For example, the largest percentage increase in U.S. pandemic-period all-cause deaths occurred in adults aged 25-44 years,<sup>9</sup> a group with low rates of COVID-19 mortality but elevated rates of anxiety and mood disorders,<sup>42</sup> suggesting possible underlying psychiatric causes. Similarly, the U.S. had the fourth-highest rate of alcohol dependence (8%) and the highest rate of opioid-related deaths (131 per million) in the world in 2016,<sup>17</sup> implicating substance-related mortality as a likely contributor to unexplained deaths. In contrast, in groups with higher rates of risk factors for COVID-19 mortality, such as obesity or smoking,<sup>4</sup> undetected COVID-19 may be a more likely cause of unexplained all-cause deaths. For example, rates of adult (aged  $\geq 15$  years) smoking in 2017 ranged from 11% or less in the U.S. and other countries (e.g., Mexico, 8%) to  $\geq 25\%$  in France, Hungary, Turkey, Greece, Russia, and Indonesia.<sup>17</sup> Similarly, within the U.S., statewide rates of obesity among adults in 2020 ranged from 24% to 40%.<sup>49</sup>

These large risk factor variations across groups and regions could represent markedly disparate true underlying causes for unexplained all-cause deaths. If so, the excess death calculation is uninterpretable when a large proportion of excess deaths is unexplained. This problem, which affected 22%-25% of the excess pandemic-period deaths measured through September 2020, suggests that excess death calculations do not consistently provide actionable information and highlights previous calls for specific,

standardized algorithms to certify mortality from respiratory illness and other causes on death certificates.<sup>1,3</sup>

Conclusion

Approximately 22%-25% of excess all-cause mortality during the U.S. 2020 COVID-19 pandemic was unexplained by changes in the top 8 causes of natural death, COVID-19, sepsis, or other respiratory illness. The onset of unexplained deaths coincided with media coverage and previously reported nationwide increases in psychotropic use. Because unexplained excess deaths may represent disparate underlying causes in different demographic groups or regions, standard excess death calculations may lack utility for evidence-based policy making. Findings highlight the need for improvements in death certification accuracy.

**Funding:** This manuscript was supported solely by Midwestern University and Kathleen Fairman LTD. The research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

**Competing Interests:** Kathleen Fairman is President and James Rucker is Research Intern with Kathleen Fairman LTD, a for-profit research consulting firm. Kathleen Fairman LTD provided analytic support and article processing charges but has no financial or nonfinancial interests related to the topic of the manuscript. Kellie Goodlet and Roy Zawadzki have no competing interests to report.

## Data Availability Statement

All source data, analytic packages, and program code for all analyses in this report are publicly available using information and links provided at

[https://github.com/JamesRucker/Unexplained\\_deaths](https://github.com/JamesRucker/Unexplained_deaths).

## Author Contributions

KAF and KJG performed concept and design, assisted by JDR and RSZ. Analyses were performed by KAF and JDR, assisted by RSZ. The manuscript was drafted by KAF and revised for important content by all authors. All authors read and approved of the final manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## Patient and Public Involvement

No patient involved. This study was a retrospective analysis of aggregated death certificate data.

## Ethics Statement

No Institutional Review Board approval or exemption was sought, as this study was a retrospective analysis of publicly available, aggregated data with no identifying information.

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Table 1. Overview of Changes in Reported Deaths During Pandemic Periods, 2019-20 Versus Prior 5-Season Benchmark

	Total	Explained			Unexplained		
	All Causes	Reported UCOD, COVID-19	Reported UCOD, Not COVID-19 <sup>a</sup>	Total Explained <sup>b</sup>	UCOD Was NEC	Unreported: All-Cause Death, No UCOD <sup>c</sup>	Total Unexplained <sup>d</sup>
<b>Pandemic awareness period<sup>e</sup></b>							
Prior-season mean benchmark	546,260	0	383,245	383,245	6,106	156,909	163,015
2019-20	560,736	3,578	384,702	388,280	6,577	165,879	172,456
Change <sup>f</sup>	<b>14,476</b>	3,578	1,457	5,035	471	8,970	9,441
% of excess deaths <sup>g</sup>	100.0%	24.7%	10.1%	34.8%	3.3%	62.0%	65.2%
<b>Initial pandemic peak period<sup>e</sup></b>							
Prior-season mean benchmark	453,618	0	315,900	315,900	5,175	132,543	137,718
2019-20	588,710	93,843	335,458	429,301	6,061	153,348	159,409
Change <sup>f</sup>	<b>135,092</b>	93,843	19,558	113,401	886	20,805	21,691
% of excess deaths <sup>g</sup>	100.0%	69.5%	14.5%	83.9%	0.7%	15.4%	16.1%
<b>Pandemic post-peak<sup>e</sup></b>							
Prior-season mean benchmark	821,482	0	565,731	565,731	9,793	245,958	255,751
2019-20	978,181	82,482	594,026	676,508	15,345	286,328	301,673
Change <sup>f</sup>	<b>156,699</b>	82,482	28,295	110,777	5,552	40,370	45,922
% of excess deaths <sup>g</sup>	100.0%	52.6%	18.1%	70.7%	3.5%	25.8%	29.3%
<b>Total changes, pandemic awareness through end of observation</b>							
Prior-season mean benchmark	1,821,360	0	1,264,876	1,264,876	21,074	535,410	556,484
2019-20	2,127,627	179,903	1,314,186	1,494,089	27,983	605,555	633,538
Change <sup>f</sup>	<b>306,267</b>	179,903	49,311	229,214	6,909	70,145	77,054
% of excess deaths <sup>g</sup>	100.0%	58.7%	16.1%	74.8%	2.3%	22.9%	25.2%

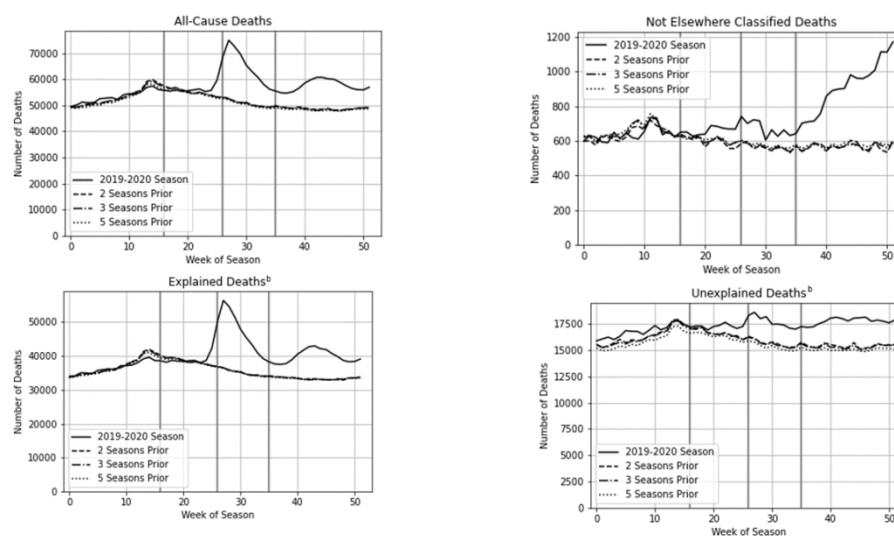
<sup>a</sup> Sum of specific causes other than COVID-19 reported in the mortality files, including heart disease, cancer, chronic lower respiratory disease, cerebrovascular disease, Alzheimer's disease, diabetes, influenza-pneumonia, other respiratory illness, kidney disease, and septicemia. Diagnosis codes for each category are in Supplement Appendix 1. <sup>b</sup> Sum of specific causes plus COVID-19. <sup>c</sup> All-cause deaths not reported in any of the categories of death included in the mortality files, including those listed in footnote a, NEC deaths, or COVID-19. <sup>d</sup> NEC deaths plus unreported deaths. Supplement Appendix 2 shows total unexplained deaths expressed as a proportion of all deaths. <sup>e</sup> Pandemic awareness is from weeks 17-26 (January 19 through March 28 in 2019-20 season). Initial pandemic peak is from weeks 27-35 (March 29 through May 30 in 2019-20 season). Pandemic post-peak is from weeks 36-52 (May 31 through September 26 in 2019-20 season). <sup>f</sup> 2019-20 values minus mean benchmark values. Summed numbers may vary by 1 from totals shown due to rounding of the population-adjusted counts. Bolded numbers are excess deaths. <sup>g</sup> Change from mean benchmark to 2019-20, expressed as a percentage of total excess all-cause deaths in 2019-20. COVID-19=coronavirus-19; NEC=not elsewhere classified; UCOD=underlying cause of death.

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Figure 1 Legend

Figure 1. Trends in Population-Adjusted Death Counts by Week of Influenza Season,<sup>a</sup> 2014-15 Through 2019-20 Seasons

<sup>a</sup> For each influenza season, week 1 begins on approximately October 1 and week 52 ends on approximately September 30. A total of 312 weeks (52 weeks for 6 seasons) were included in the analyses. Dividing lines represent the ends of weeks 16 (week prior to pandemic awareness period), 26 (week prior to initial pandemic peak), and 35 (week prior to pandemic post-peak period). Prior-season benchmarks are means (deaths summed across seasons, divided by 2, 3, and 5, respectively, for 2-season, 3-season, and 5-season benchmarks). Benchmarks for 2, 3, and 5 seasons, respectively, are indicated by long dashed lines, alternating short and long dashed lines, and dotted lines. <sup>b</sup> Explained deaths include specific causes reported in the mortality files, including heart disease, cancer, chronic lower respiratory disease, cerebrovascular disease, Alzheimer’s disease, diabetes, influenza-pneumonia, other respiratory illness, kidney disease, septicemia, and COVID-19. Diagnosis codes for each category are in Supplement Appendix 1. Unexplained deaths are all-cause deaths with no reported underlying cause or with a not elsewhere classified (NEC) cause (all-cause deaths minus explained deaths). NEC deaths are described in ICD-10 nomenclature as “symptoms, signs, and abnormal clinical and laboratory findings not elsewhere classified” (ICD-10 range R00-R99), include “ill-defined and unknown cause of mortality” (R99), a code commonly used pending forensic investigation of injurious death.<sup>24,25</sup> COVID-19=coronavirus-19; ICD=International Classification of Diseases; NEC=not elsewhere classified.



855x481mm (38 x 38 DPI)

Appendix 1. ICD-10 Category Descriptions in NCHS Files, Ranked in Descending Order by U.S. Death Counts in 2017<sup>8</sup>

NCHS Category: Diseases of the Heart (I00-I09; I11 I13; I20-I51)	
I00-I02 Acute rheumatic fever	
I05-I09 Chronic rheumatic heart diseases;	
I11 Hypertensive heart disease	
I13 Hypertensive heart and chronic kidney disease	
I20 Angina pectoris	
I21 Acute myocardial infarction	
I22 Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction	
I23 Certain complications following ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction (within the 28 day period)	
I24 Other acute ischemic heart diseases	
I25 Chronic ischemic heart disease	
I26-I28 Pulmonary heart disease and diseases of pulmonary circulation	
I30 Acute pericarditis	
I31 Other diseases of pericardium	
I32 Pericarditis in diseases classified elsewhere	
I33 Acute and subacute endocarditis	
I34 Nonrheumatic mitral valve disorders	
I35 Nonrheumatic aortic valve disorders	
I36 Nonrheumatic tricuspid valve disorders	
I37 Nonrheumatic pulmonary valve disorders	
I38 Endocarditis, valve unspecified	
I39 Endocarditis and heart valve disorders in diseases classified elsewhere	
I40 Acute myocarditis	
I41 Myocarditis in diseases classified elsewhere	
I42 Cardiomyopathy	
I43 Cardiomyopathy in diseases classified elsewhere	
I44 Atrioventricular and left bundle-branch block	
I45 Other conduction disorders	
I46 Cardiac arrest	
I47 Paroxysmal tachycardia	
I48 Atrial fibrillation and flutter	
I49 Other cardiac arrhythmias	
I50 Heart failure	
I51 Complications and ill-defined descriptions of heart disease	
NCHS Category: Malignant Neoplasms (C00-C97)	
Code range includes malignant neoplasms of all types	
NCHS Category: Chronic Lower Respiratory Disease (J40-J47)	
J40 Bronchitis, not specified as acute or chronic	
J41 Simple and mucopurulent chronic bronchitis	
J42 Unspecified chronic bronchitis	
J43 Emphysema	
J44 Other chronic obstructive pulmonary disease	
J45 Asthma	
J46 Status asthmaticus	
J47 Bronchiectasis	
NCHS Category: Cerebrovascular Disease (I60-I69)	
I60 Nontraumatic subarachnoid hemorrhage	
I61 Nontraumatic intracerebral hemorrhage	
I62 Other and unspecified nontraumatic intracranial hemorrhage	
I63 Cerebral infarction	
I64 Stroke, not specified if hemorrhagic or infarct	

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4	I65 Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction
5	I66 Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction
6	I67 Other cerebrovascular diseases
7	I68 Cerebrovascular disorders in diseases classified elsewhere
8	I69 Sequelae of cerebrovascular disease
9	<b>NCHS Category: Alzheimer's Disease (G30)</b>
10	G30 Alzheimer's disease
11	<b>NCHS Category: Diabetes (E10-E14)</b>
12	E10 Type 1 diabetes mellitus
13	E11 Type 2 diabetes mellitus
14	E13 Other specified diabetes mellitus
15	E14 is an old code for unspecified diabetes mellitus
16	<b>NCHS Category: Influenza and Pneumonia (J10-J18)</b>
17	J10 Influenza due to other identified influenza virus
18	J11 Influenza due to unidentified influenza virus
19	J12 Viral pneumonia, not elsewhere classified
20	J13 Pneumonia due to Streptococcus pneumoniae
21	J14 Pneumonia due to Hemophilus influenzae
22	J15 Bacterial pneumonia, not elsewhere classified
23	J16 Pneumonia due to other infectious organisms, not elsewhere classified
24	J17 Pneumonia in diseases classified elsewhere
25	J18 Pneumonia, unspecified organism
26	<b>NCHS Category: Nephritis, Nephrotic Syndrome, and Nephrosis (N00-N07, N17-N19, N25-N27)</b>
27	N00 Acute nephritic syndrome
28	N01 Rapidly progressive nephritic syndrome
29	N02 Recurrent and persistent hematuria
30	N03 Chronic nephritic syndrome
31	N04 Nephrotic syndrome
32	N05 Unspecified nephritic syndrome
33	N06 Isolated proteinuria with specified morphological lesion
34	N07 Hereditary nephropathy, not elsewhere classified
35	N17 Acute kidney failure
36	N18 Chronic kidney disease
37	N19 Unspecified kidney failure
38	N25 Disorders resulting from impaired renal tubular function
39	N26 Unspecified contracted kidney
40	N27 Small kidney of unknown cause
41	<b>NCHS Category: Other Diseases of the Respiratory System (J00-J06,J30-J39,J67,J70-J98)</b>
42	J00 Acute nasopharyngitis [common cold]
43	J01 Acute sinusitis
44	J02 Acute pharyngitis
45	J03 Acute tonsillitis
46	J04 Acute laryngitis and tracheitis
47	J05 Acute obstructive laryngitis [croup] and epiglottitis
48	J06 Acute upper respiratory infections of multiple and unspecified sites
49	J30 Vasomotor and allergic rhinitis
50	J31 Chronic rhinitis, nasopharyngitis and pharyngitis
51	J32 Chronic sinusitis
52	J33 Nasal polyp
53	J34 Other and unspecified disorders of nose and nasal sinuses
54	J35 Chronic diseases of tonsils and adenoids
55	J36 Peritonsillar abscess
56	J37 Chronic laryngitis and laryngotracheitis
57	J38 Diseases of vocal cords and larynx, not elsewhere classified
58	J39 Other diseases of upper respiratory tract

J67	Hypersensitivity pneumonitis due to organic dust
J70	Respiratory conditions due to other external agents
J80	Acute respiratory distress syndrome
J81	Pulmonary edema
J82	Pulmonary eosinophilia, not elsewhere classified
J84	Other interstitial pulmonary diseases
J85	Abscess of lung and mediastinum
J86	Pyothorax
J90	Pleural effusion, not elsewhere classified
J91	Pleural effusion in conditions classified elsewhere
J92	Pleural plaque
J93	Pneumothorax and air leak
J94	Other pleural conditions
J95-J95	Intraoperative and postprocedural complications and disorders of respiratory system, not elsewhere classified
J96	Respiratory failure, not elsewhere classified
J98	Other respiratory disorders
<b>NCHS Category: Septicemia (A40-A41)</b>	
A40	Streptococcal sepsis
A41	Other sepsis
<b>NCHS Category: Symptoms, Signs, and Abnormal Clinical and Laboratory Findings (R00-R99)</b>	
R00-R09	Symptoms and signs involving the circulatory and respiratory systems
R10-R19	Symptoms and signs involving the digestive system and abdomen
R20-R23	Symptoms and signs involving the skin and subcutaneous tissue
R25-R29	Symptoms and signs involving the nervous and musculoskeletal systems
R30-R39	Symptoms and signs involving the genitourinary system
R40-R46	Symptoms and signs involving cognition, perception, emotional state and behavior
R47-R49	Symptoms and signs involving speech and voice
R50-R69	General symptoms and signs
R70-R79	Abnormal findings on examination of blood, without diagnosis
R80-R82	Abnormal findings on examination of urine, without diagnosis
R83-R89	Abnormal findings on examination of other body fluids, substances and tissues, without diagnosis
R90-R94	Abnormal findings on diagnostic imaging and in function studies, without diagnosis
R97-R97	Abnormal tumor markers
R99-R99	Ill-defined and unknown cause of mortality
<b>NCHS Category: COVID-19</b>	
U071	COVID-19

COVID-19=coronavirus-19; ICD=International Classification of Diseases codes available at <https://www.icd10data.com/>;  
NCHS=National Center for Health Statistics

## Appendix 2. Relative Changes in Explained Versus Unexplained Deaths by Time Period, 2019-20 Versus Prior 5-Season Benchmark

	Total All-Cause Deaths	Total Explained Deaths <sup>a</sup>	Total Unexplained Deaths <sup>a</sup>	Unexplained (% of Total Deaths)
<b>Pandemic awareness<sup>b</sup></b>				
Prior season mean benchmark	546,260	383,245	163,015	29.8
2019-20	560,736	388,280	172,456	30.8
% change from benchmark to 2019-20	2.7%	1.3%	5.8%	--
<b>Initial pandemic peak period<sup>c</sup></b>				
Prior season mean benchmark	453,618	315,900	137,718	30.4
2019-20	588,710	429,301	159,409	27.1
% change from benchmark to 2019-20	29.8%	35.9%	15.8%	--
<b>Pandemic post-peak<sup>d</sup></b>				
Prior season mean benchmark	821,482	565,731	255,751	31.1
2019-20	978,181	676,508	301,673	30.8
% change from benchmark to 2019-20	19.1%	19.6%	18.0%	--
<b>Total, pandemic awareness through end of observation</b>				
Prior season mean benchmark	1,821,360	1,264,876	556,484	30.6
2019-20	2,127,627	1,494,089	633,538	29.8
% change from benchmark to 2019-20	16.8%	18.1%	13.8%	--

<sup>a</sup> Explained deaths are all-cause deaths reported in the specific categories of death included in the mortality files, including coronavirus-19. Unexplained deaths are all-cause deaths not reported in any of the categories of death included in the mortality files, plus deaths recorded as not elsewhere classified. <sup>b</sup> Weeks 17-26 (January 19 through March 28 in 2019-20 season). <sup>c</sup> Weeks 27-35 (March 29 through May 30 in 2019-20 season). <sup>d</sup> Weeks 36-52 (May 31 through September 26 in 2019-20 season).

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Appendix 3. Overview of Changes in Reported Deaths During Pandemic Periods, 2019-20 Versus Prior 2-Season and 3-Season Benchmarks

	Total	Explained			Unexplained		
	All Causes	Reported UCOD, COVID-19	Reported UCOD, Not COVID-19 <sup>a</sup>	Total Explained <sup>b</sup>	UCOD Was NEC	Unreported: All-Cause Death, No UCOD <sup>c</sup>	Total Unexplained <sup>d</sup>
<b>Pandemic awareness period<sup>e</sup></b>							
Prior-season mean, 2-season benchmark	551,845	0	385,438	385,438	5,971	160,437	166,408
Prior-season mean, 3-season benchmark	551,951	0	385,863	385,863	6,058	160,030	166,088
2019-20	560,736	3,578	384,702	388,280	6,577	165,879	172,456
Change, 2-season benchmark <sup>f</sup>	<b>8,891</b>	3,578	-736	2,842	606	5,442	6,048
Change, 3-season benchmark <sup>f</sup>	<b>8,785</b>	3,578	-1,161	2,417	519	5,849	6,368
% of excess deaths, 2-season benchmark	100.0%	40.2%	-8.3%	32.0%	6.8%	61.2%	68.0%
% of excess deaths, 3-season benchmark	100.0%	40.7%	-13.2%	27.5%	5.9%	66.6%	72.5%
<b>Initial pandemic peak period<sup>e</sup></b>							
Prior-season mean, 2-season benchmark	458,044	0	317,107	317,107	5,051	135,886	140,937
Prior-season mean, 3-season benchmark	457,300	0	316,944	316,944	5,096	135,260	140,356
2019-20	588,710	93,843	335,458	429,301	6,061	153,348	159,409
Change, 2-season benchmark <sup>f</sup>	<b>130,666</b>	93,843	18,351	112,194	1,010	17,462	18,472
Change, 3-season benchmark <sup>f</sup>	<b>131,410</b>	93,843	18,514	112,357	965	18,088	19,053
% of excess deaths, 2-season benchmark	100.0%	71.8%	14.0%	85.9%	0.8%	13.4%	14.1%
% of excess deaths, 3-season benchmark	100.0%	71.4%	14.1%	85.5%	0.7%	13.8%	14.5%
<b>Pandemic post-peak<sup>e</sup></b>							
Prior-season mean, 2-season benchmark	829,780	0	567,619	567,619	9,639	252,522	262,161
Prior-season mean, 3-season benchmark	827,727	0	567,244	567,244	9,634	250,850	260,484
2019-20	978,181	82,482	594,026	676,508	15,345	286,328	301,673
Change, 2-season benchmark <sup>f</sup>	<b>148,401</b>	82,482	26,407	108,889	5,706	33,806	39,512
Change, 3-season benchmark <sup>f</sup>	<b>150,454</b>	82,482	26,782	109,264	5,711	35,478	41,189
% of excess deaths, 2-season benchmark	100.0%	55.6%	17.8%	73.4%	3.8%	22.8%	26.6%
% of excess deaths, 3-season benchmark	100.0%	54.8%	17.8%	72.6%	3.8%	23.6%	27.4%
<b>Total changes, pandemic awareness through end of observation</b>							
2-season benchmark <sup>f</sup>	<b>287,957</b>	179,903	44,022	223,925	7,322	56,709	64,032
% of excess deaths, 2-season benchmark	100.0%	62.5%	15.3%	77.8%	2.5%	19.7%	22.2%
3-season benchmark <sup>f</sup>	<b>290,649</b>	179,903	44,136	224,039	7,195	59,415	66,610
% of excess deaths, 3-season benchmark	100.0%	61.9%	15.2%	77.1%	2.5%	20.4%	22.9%

<sup>a</sup> Sum of specific causes other than COVID-19 reported in the mortality files, including heart disease, cancer, chronic lower respiratory disease, cerebrovascular disease, Alzheimer's disease, diabetes, influenza-pneumonia, other respiratory illness, kidney disease, and septicemia. Diagnosis codes for each category are in Appendix 1. <sup>b</sup> Sum of specific causes plus COVID-19. <sup>c</sup> All-cause deaths not reported in any of the categories of death included in the mortality files, including those listed in footnote a, NEC deaths, or COVID-19. <sup>d</sup> NEC deaths plus unreported deaths. <sup>e</sup> Pandemic awareness is from weeks 17-26 (January 19 through March 28 in 2019-20 season). Initial pandemic peak is from weeks 27-35 (March 29 through May 30 in 2019-20 season). Pandemic post-peak is from weeks 36-52 (May 31 through September 26 in 2019-20 season). <sup>f</sup> 2019-20 values minus benchmark values. Bolded numbers are excess deaths. COVID-19=coronavirus-19; NEC=not elsewhere classified; UCOD=underlying cause of death.

## STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1	Retrospective Analysis of Death Certificate Data
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2	Outcome Measures: Change in population-adjusted counts of deaths from seasonal benchmarks to 2019-20, from all causes (i.e., total excess deaths) and from explained versus unexplained causes, reported for the season overall and for time periods defined <i>a priori</i> Results: 287,957-306,267 excess deaths occurred through September 2020: 179,903 (58.7%-62.5%) attributed to COVID-19; 44,022-49,311 (15.2%-16.1%) to other reported causes; 64,032-77,054 (22.2%-25.2%) unexplained (unspecified or unreported cause)... Unexplained deaths constituted 65.2%-72.5% of excess deaths from January 19 to March 28 and 14.1%-16.1% from March 29 through May 30.
<b>Introduction</b>				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-7	<i>See text on rationale for use of excess death calculation, various potential interpretations for unexplained deaths, and need to quantify the proportion of excess mortality due to unexplained changes in mortality.</i>
Objectives	3	State specific objectives, including any prespecified hypotheses	7	The primary research question was to what degree unexplained mortality contributed to excess mortality during the pandemic. ... A secondary research question, intended to provide exploratory information about possible reasons for unexplained mortality, was when unexplained deaths escalated in 2020.
<b>Methods</b>				
Study design	4	Present key elements of study design early in the paper	7	This study was a retrospective, repeated cross-sectional analysis of U.S. mortality files made available by the NCHS
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-9	<i>See Design and Data Source section; first sentence of Data Analyses section</i>
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and	7,9	<i>No participants. All deaths in 2020, representing provisional causes of death; and 2014-2019, representing final causes of death, except for two states with incomplete reporting, were analyzed. Data from October 5, 2014, through September 26, 2020, were downloaded on January 22, 2021. ... As in previous research,</i>

		control selection. Give the rationale for the choice of cases and controls		Connecticut and North Carolina were excluded because of incomplete reporting. <sup>8</sup>
		<i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants		
		<i>(b) Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed		
		<i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8; Appendix 1	The study measures were based on reported underlying cause of death (UCOD), defined as “the disease or injury which initiated the train of morbid events leading directly to death.” <sup>22</sup> Only one UCOD is reported on each death certificate. The study files include weekly counts of deaths in total (all-cause) and by UCOD category, grouped by state.
				In addition to categories representing the top 8 U.S. causes of natural death (heart disease, cancer, chronic lower respiratory disease, cerebrovascular disease, Alzheimer’s disease, diabetes, influenza and pneumonia, and kidney disease), which together accounted for 66% of all U.S. deaths in 2017, <sup>23</sup> the files include four additional categories: miscellaneous respiratory conditions, (e.g., nasopharyngitis, sinusitis, pneumothorax); septicemia; COVID-19; and nonspecific-cause deaths. <sup>13,14</sup>
				<i>Diagnosis codes are shown in Appendix 1.</i>
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8 9-10	<i>Design and Data Source section. Only one group. Data Analyses—methods of parsing deaths by time period and into explained and unexplained proportions</i>
Bias	9	Describe any efforts to address potential sources of bias	9	For each week, time period, and diagnostic category, we calculated prior-season averages for 3 historical benchmark periods: 2 seasons (2017-18 to 2018-19), 3 seasons (2016-17 to 2018-19), and 5 seasons (2014-15 to 2018-19). ... Three benchmark time periods were used because it is common to compare current-year mortality data with several historical benchmarks, <sup>31</sup> consistent with the need to report sensitivity analyses of epidemiological data. <sup>32</sup>
Study size	10	Explain how the study size was arrived at	Inapplicable	<i>Population data; no sampling</i>

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9	Analyses were performed using open-source analytic tools. <sup>11</sup> Specifically, Python coding was used with Pandas, a data-organization tool, <sup>26,27</sup> to group data into 6 influenza seasons, 52 weeks each. Using the same software tools, data for the 2014-15 to 2018-19 seasons were population-adjusted to July 2019 using U.S. Census data. <sup>11,28</sup> ... Data were further grouped <i>a priori</i> into time periods roughly corresponding to U.S. trends in COVID-19 mortality...
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	9-10	For each week, time period, and diagnostic category, we calculated prior-season averages for 3 historical benchmark periods: 2 seasons (2017-18 to 2018-19), 3 seasons (2016-17 to 2018-19), and 5 seasons (2014-15 to 2018-19). ... For each week and time period, excess deaths were defined <i>a priori</i> as increases in all-cause deaths over the population-adjusted prior-season mean benchmarks (i.e., 2019-20 season values minus benchmark values). Unexplained deaths were defined as all-cause deaths either not reported in any diagnostic category (unreported) or reported in the NEC category (unspecified).
		(b) Describe any methods used to examine subgroups and interactions	Inapplicable	No analyses of subgroups or interactions
		(c) Explain how missing data were addressed	Inapplicable	No missing data other than in the two states excluded from the analysis due to incomplete reporting
		(d) Cohort study—If applicable, explain how loss to follow-up was addressed Case-control study—If applicable, explain how matching of cases and controls was addressed Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	Inapplicable	No loss to follow-up, as study was a retrospective analysis of a dataset that included aggregated counts of deaths
		(e) Describe any sensitivity analyses	9	Three benchmark time periods were used because it is common to compare current-year mortality data with several historical benchmarks, <sup>31</sup> consistent with the need to report sensitivity analyses of epidemiological data. <sup>32</sup>
<b>Results</b>				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10	Except for 2 states with incomplete reporting, there were no exclusion criteria in this study. As population data were used, there were no sampling stages.

		(b) Give reasons for non-participation at each stage		<i>No participants and no nonparticipation, as study was a retrospective analysis of a dataset that included aggregated counts of deaths.</i>
		(c) Consider use of a flow diagram		
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10	Of a total of 16.3 million all-cause deaths reported over 6 influenza seasons in 48 states, 2.98 million occurred during 2019-20, representing a population-adjusted increase of 288,467-319,858 excess deaths over prior-season averages for 2, 3, and 5 years (Figure 1, top). Mean annual population-adjusted total all-cause death counts varied modestly across seasonal benchmarks, ranging from 2,659,228 to 2,690,619.
		(b) Indicate number of participants with missing data for each variable of interest	Inapplicable	<i>No missing data other than in the two states excluded from the analysis due to incomplete reporting. Absence of a specific cause of death was the study outcome measure.</i>
		(c) Cohort study—Summarise follow-up time (eg, average and total amount)		
Outcome data	15*	Cohort study—Report numbers of outcome events or summary measures over time		
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study—Report numbers of outcome events or summary measures	10	Of a total of 16.3 million all-cause deaths reported over 6 influenza seasons in 48 states, 2.98 million occurred during 2019-20, representing a population-adjusted increase of 288,467-319,858 excess deaths over prior-season averages for 2, 3, and 5 years (Figure 1, top). Mean annual population-adjusted total all-cause death counts varied modestly across seasonal benchmarks, ranging from 2,659,228 to 2,690,619.
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-11	<i>No statistical adjustments, no sampling, population data</i> Contribution of unexplained mortality to excess deaths varied considerably by pandemic period (Table 1; Supplement Appendix 2). Using the 5-year benchmark, of the total increase of 306,267 all-cause deaths reported from pandemic awareness through end of observation (seasonal weeks 17-52, January 19 through September 26, 2020), 179,903 (58.7%) were attributed to COVID-19; 49,311 (16.1%) to changes in reported causes other than COVID-19; 6,909 (2.3%) to increased NEC deaths; and 70,145 (22.9%) to increases in deaths with no reported cause. On a proportional basis, mortality change with unexplained (unreported or NEC) cause was much greater in the pandemic awareness period (January 19 through March 28, 65.2% of

				change in all-cause deaths) than in the initial pandemic peak period (March 29 through May 30, 16.1%) or the post-peak period (May 31 through September 26, 29.3%). In total, an increase of 77,054 unexplained deaths was responsible for 25.2% of change in all-cause mortality from January 19 through September 26, 2020.
		(b) Report category boundaries when continuous variables were categorized	Inapplicable	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Inapplicable	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11	Results using the 2- and 3-year benchmarks were similar (Supplement Appendix 3). Using these benchmarks, increases in unexplained deaths accounted for 68.0%-72.5% of excess deaths during the pandemic awareness period; 14.1%-14.5% of excess deaths during initial peak; and 26.6%-27.4% of excess deaths in the pandemic post-peak period. Measured from pandemic awareness through the end of observation, changes in unexplained deaths accounted for 22.2%-22.9% of excess deaths.
<b>Discussion</b>				
Key results	18	Summarise key results with reference to study objectives	11	This analysis of population-adjusted U.S. death certificate data for 6 influenza seasons, the first to assess the extent and timing of unexplained pandemic deaths, indicated substantial impact of unexplained deaths on excess pandemic-period mortality.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11-12	The most important study limitation is that observation ended on September 26, 2020. Results may not apply to subsequent disease activity, including the surge late in 2020, or to other countries. <sup>29</sup> Additionally, this analysis was descriptive, although it produced results for all-cause deaths similar to those using more sophisticated statistical methods. <sup>8,9</sup> For example, the 299,028 excess deaths estimated by the CDC using Poisson regression modeling through October 3, 2020 <sup>9</sup> is comparable to our estimate of 287,957-306,267 excess deaths through September 26, 2020.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-16	Despite these limitations, the finding that a large proportion of 2020 excess mortality was unexplained by changes in top causes of natural death or respiratory disease suggests a need to extend thinking about pandemic mortality beyond COVID-19 or its physical sequelae.
				<i>See discussions of possibility that drug overdoses and suicides may have contributed to unexplained mortality (page 12-13);</i>

				<i>need to explore effects of role of media coverage and other societal causes (page 14); possibility that underlying causes of unexplained deaths vary by demographic group or region (page 15-16).</i>
Generalisability	21	Discuss the generalisability (external validity) of the study results	12	Results may not apply to subsequent disease activity, including the surge late in 2020, <sup>29</sup> or to other countries.
<b>Other information</b>				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16	<b>Funding:</b> This manuscript was supported solely by Midwestern University and Kathleen Fairman LTD. The research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. <b>Competing Interests:</b> Kathleen Fairman is President and James Rucker is Research Intern with Kathleen Fairman LTD, a for-profit research consulting firm. Kathleen Fairman LTD provided analytic support and article processing charges but has no financial or nonfinancial interests related to the topic of the manuscript. Kellie Goodlet and Roy Zawadzki have no competing interests to report.

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).